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ORIGINAL ARTICLE

Factors predicting non-sentinel lymph node metastasis in T1-2 invasive breast cancer with 1-2 axillary sentinel lymph node metastases: Presentation of Ondokuz Mayis scoring system

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Summary

Purpose: *To evaluate the predicting factors for non-sentinel lymph node (SLN) metastases in T1-2 invasive breast cancer with 1-2 metastatic SLN that fully matched the ACOSOG Z0011 criteria. Also, to develop a scoring system to predict the risk of non-SLN metastasis and to discriminate the low-risk patients for omission of the axillary lymph node dissection (ALND) in this population.*

Methods: *Two hundred and seven T1-2 invasive breast cancer patients with 1-2 metastatic SLN who underwent ALND at our Institution were included in the study. Independent factors predicting the non-SLN metastasis were found using logistic regression analysis, and a scoring system to predict the non-SLN metastasis was created.*

Results: *Seventy (34%) out of 207 patients had non-SLN metastasis. Multivariate logistic regression analysis demonstrated that tumor size, presence of lymphovascular invasion (LVI), number of negative SLNs, and size of SLN metastasis were independent factors predicting non-SLN metastasis. There were 68 (33%) and 108 (52%) patients with a the score of ≤ 4 (predicted probability of ≤10%) with a false negative rate (FNR) of 4.4%, and ≤5 (predicted probability of ≤15%) with a FNR of 7.4%, respectively. The area under the curve (AUC) value for the Ondokuz Mayis scoring system was 0.88 (95% CI 0.83-0.93).*

Conclusions: *The present Ondokuz Mayis model with an AUC of 0.88 showed excellent discrimination capacity to distinguish patients at low risk for positive non-SLN from high risk patients and could help spare ALND in an important portion of patients.*

Key words: *axillary scoring system, invasive breast cancer, non-sentinel lymh node metastasis, sentinel node metastasis*

Introduction

The American College of Surgeons (ACOSOG) Z0011 trial showed that in clinically node-negative women undergoing breast-conserving therapy (BCT) for invasive breast cancer, omission of ALND in T1-2 breast cancers with 1-2 metastatic SLN and without extranodal extension (ENE) had not decreased survival, not increased axillary recurrence, and decreased morbidity compared with axillary dissection [1]. This study changed the practice of ALND and breast surgeons in some main breast cancer Centers began to omit the ALND in breast cancer patients with T1-2 tumor and with ≤ 2 SLNs and without ENE who underwent breast-conserving surgery after its publication [2-4]. The National Comprehensive Cancer Network (NCCN) recommended no ALND following sentinel lymph node biopsy (SLNB) for patients meeting the ACOSOG Z0011 eligibility

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criteria [5]. American Society of Clinical Oncology (ASCO) also did not recommend routine ALND based on the ACOSOG Z00011 study [6].

However, the long-term recurrence-free survival in patients treated according to ACOSOG Z0011 is not known and it could be argued that the residual non-SLN could increase the axillary recurrence. Invasive breast cancer patients with T1-2 tumors who underwent mastectomy and had 1-2 metastatic SLN could also be considered for not having ALND if predicting factors for non-SLN have been known. On the other hand, the EBCCG study demonstrated that local-regional recurrence had long-term unfavorable effect on survival [7]. Therefore, knowing the predictive factors for non-SLN metastasis in 1-2 SLN positive breast cancer, the probable axillary recurrence could be prevented by ALND for this subgroup of patients. Predicting factors for non-SLN metastasis in 1-2 SLN positive breast cancer have also been investigated in three studies from China [8-10]. However, either the results found remained unsatisfactory for predicting the status of non-SLN [8] or the sample size was small to reach sound conclusions [9]. There was only one study with a large sample size to predict the non-SLN metastasis in breast cancer patients with 1-2 positive SLN [10], and the Shangai Cancer Center non-SLN nomogram was the only nomogram created by the factors from that study to discriminate the low-risk patients for whom ALND might be omitted [10]. However, none of these studies were performed among patients who fully matched the Z0011 criteria.

The present study was planned to evaluate the predictive factors for non-SLN metastases in T1-2 breast cancers with 1-2 SLN positive nodes and without ENE that fully matched the Z0011 criteria. Also, a scoring system was developed to predict the risk of non-SLN metastasis and to discriminate the low-risk patients for omission of the ALND in this population.

Methods

Two hundred and seven invasive breast cancer patients with metastatic SLNB who underwent ALND between 2003 and 2016 at the Department of General Surgery, Ondokuz Mayis University School of Medicine were included in the study. Breast cancer patients with T1-2 tumors and with 1-2 metastatic SLN and without ENE were the subjects of the present study. Patients with > 2 metastatic SLNs, with ENE, with multicentric tumors, and patients with SLNs detected by immunohistochemistry (IHC) were excluded. The patients included in this study were selected from 1074 invasive breast cancer patients with T1-3 tumors and clinically negative axilla who had not received neoadjuvant chemotherapy and who underwent SLNB and breast-conserving surgery or mastectomy. This study followed the principles of the Declaration of Helsinki of 1975, as revised in 2000.

The probable predictive factors for non-SLN metastasis were defined as: age (<50, ≥50 years), pathological tumor size (pT) (≤1, 1.1-2, 2.1-3, 3.1-5, and >5 cm), histological type (invasive ductal, invasive lobular), histological grade (ductal 1, ductal 2, ductal 3, lobular), LVI (absent, present), number of SLNs, number of positive SLNs (posSLN) (1,2), number of negative SLNs (negSLN) (0, 1, 2, ≥3), ratio of positive SLNs to total SLNs (pos ratio) (<0.5, ≥0.5-<1, 1), the size of the largest SLN metastasis (SLNMS) (≤2, >2-5, >5-10, and >10 mm), the ER status (negative, positive), the PR status (negative, positive) and the c-erbB2 receptor status (negative, positive) (Table 1).

Patients underwent SLNB with 5 mL injectable sterile solution of 1% isosulphan blue. Patients with SLN metastases in frozen sections underwent immediate ALND, and patients found to have SLN metastasis by routine or serial section H&E staining later underwent a second surgery for ALND. All SLNs were sent for frozen analysis. If the SLN size was ≤1 cm, it was bisected parallel to the long axis. An imprint was applied for two cut surfaces, which then underwent frozen sectioning. The frozen sections and imprint preparates were stained with H&E and analyzed under a microscope. If the SLN was >1 cm, it was cut into slices perpendicular to the long axis at 2 mm intervals. All cut surfaces underwent imprint and frozen analyses. If the SLN contained apparent metastases at the macroscopic evaluation, only the imprint analysis was performed. After the frozen section analysis, the remaining frozen tissue was fixed in formalin and embedded in paraffin for routine pathological examination. The non-SLNs that were ≤1 cm obtained from ALND were bisected parallel to the long axis and the non-SLNs that were >1 cm were cut into slices perpendicular to the long axis at 2 mm intervals. The evaluation of non-SLNs was usually performed only by H&E staining, and serial sectioning or immunohistochemistry were not routinely performed.

Probable predictive factors which were found to be significantly associated with non-SLN metastasis in univariate analysis, entered in multivariate logistic regression analysis. Independent predictive factors and predictive probabilities of non-SLN metastasis were found by backward logistic regression analysis. Using four independent factors (pT, LVI, negSLN and SLNMS) for non-SLN metastasis we created a predictive scoring system to predict the non-SLN metastasis. The categories of pT, LVI, negSLN and SLNMS were scored from 0 to 4 and thus risk scores were obtained for each patient. pT categories (≤1 cm, 1.1-2 cm, 2.1-3 cm, 3.1-5 cm, >5 cm) were scored as 0, 1, 2, 3, and 4, LVI (absent, pres-

Table 1. Comparison of patient and tumor characteristics by positive non-SLNs

Characteristics	*Number (%)*	*Number of positive non-SLN (%)*	*P Univariate*	*P Multivariate*
Age, years				
≤50	126 (61)	50 (40)	0.035	NS
>50	81(39)	20 (25)		
Pathological tumor size (pT), cm				
≤1	33 (16)	2 (6)	<0.001	< 0.001
1.1-2	73 (35)	16 (22)		
2.1-3	53 (26)	19 (36)		
3.1-5	48 (23)	33 (69)		
Histological type				
Invasive ductal	182 (88)	58 (32)	0.11	NS
Invasive lobular	25 (12)	12 (48)		
Tumor type and histological grade				
Ductal 1	18 (9)	0 (0)		
Ductal 2	121 (58)	40 (33)	0.002	NS
Ductal 3	43 (21)	18 (42)		
Lobular	25 (12)	12 (48)		
Lymphovascular invasion				
Absent	120 (58)	19 (16)	<0.001	0.013
Present	87 (42)	51 (59)		
Estrogen receptor				
Negative	25 (12) 182 (88)	7 (28)	0.65	NS
Positive		63 (35)		
Progesterone receptor				
Negative	61 (24) 146 (76)	18 (30)	0.42	NS
Positive		52 (36)		
c-erb B2 receptor				
Negative	169 (82)	56 (33)		
Positive	38 (18)	14 (37)	0.70	NS
pRatio				
<0.5	54 (26)	11 (20)	<0.001	NS
≥0.5-<1	70 (34)	17 (24)		
1	83 (40)	42 (51)		
Number of positive SLNs				
1	137 (66)	49 (36)	0.44	NS
2	70 (34)	21 (30)		
Number of negative SLNs				
0	81 (39)	42 (52)	<0.001	0.01
1	66 (32)	19 (29)		
2	28 (14)	6 (21)		
≥3	32 (15)	3 (9)		
Number of SLNs				
1	49 (24)	29 (59)	<0.001	NS
2	70 (34)	22 (31)		
3	48 (23)	16 (33)		
4	31 (15)	1 (33)		
5	9 (4)	2 (22)		
SLN largest metastasis size, mm				
≤ 2	39 (19)	1 (2.6)	<0.001	< 0.001
> 2 - 5	53 (26)	10 (19)		
> 5 - 10	70 (34)	27 (39)		
> 10	45 (22)	32 (71)		

pRatio: ratio of metastatic SLNs to total SLNs, SLN: sentinel lymph node, NS: not significant

ent) as 0 and 1, number of negative SLNs (negSLN) (≥ 3, 2, 1, 0) as 0, 1, 2, and 3, and SLNMS (≤ 2 mm, > 2 - 5 mm, > 5-10 mm, > 10 mm) categories as 0, 1, 2, and 3 risk scores, respectively. Cumulative risk scores which were estimated from the sum of the risk scores of 0 to 4 from each category of risk factors for each patient were classified as predictive risk scores of 0 to 10 (Table 3).

Receiver operating characteristics (ROC) curve was generated and the AUC was calculated for assessing the discrimination of the model [11]. AUC varies between 0.5 and 1.0, and the higher the better. Discrimination which refers to the ability to distinguish high risk pa-

tients for positive non-SLN from low risk patients was quantified by AUC [12]. The number and proportion of patients and FNR at various predictive risk scores and cut-off levels were also calculated for Ondokuz Mayis scoring system. Calibration (ie, the ability of a predictive model to match predicted and observed probabilities or the accuracy of positive non-SLN risk prediction) was assessed graphically. The predicted probabilities were categorized into 10 deciles, and the observed percentage of positive non-SLN for each decile (actual probability) was calculated. Using the actual probability for Y axis, and the predictive probabilities at X axis, the calibration curve was generated. FNR were estimated as the number of patients with non-SLN metastasis by the number of the patients for each predictive risk scores.

Statistics

The factors for comparison were recorded on a computer using Statistical Program for Social Science (SPSS) version 15.0. Categorical data were expressed as numbers and percentages, and continuous data were expressed as medians and ranges. Comparisons of positive non-SLNs with categorical data were performed using chi-square test. A p value <0.05 was accepted as significant. Multivariate analysis was performed using logistic regression analysis and odds ratios (OR) for positive non-SLNs, and the 95% confidence intervals (CI) were calculated. The calibration of the Ondokuz Mayis nomogram was evaluated using the Hosmer-Lemeshow goodness-of-fit test and visually by plots [13].

Results

The median patient age was 49 years (range 27-76), and the median number of axillary nodes removed was 14 (range 7-42). The median number of SLNs was 2 (range 1-5) and the median number of removed non-SLNs and metastatic non-SLNs were 10 (range 0-38) and 3 (range 1-22), respectively. The median size of the SLN metastases was 7 mm (range 1-24). While 70 (34%) out of 207 patients with 1-2 SLN metastasis had non-SLN metastasis, 137 (66%) had not. One hundred and eighteen patients (57%) underwent BCS and 89 (43%) mastectomy. Two hundred (97%) SLN metastases were detected in the frozen sections, 7 at routine H&E.

By univariate analysis, pT (p<0.001), LVI (p<0.001), SLNs (p<0.001), negSLN (p<0.001), SLNMS (p<0.001), pRatio (p<0.001), and grade (p=0.025) were found to be significantly associated with non-SLN metastasis (Table 1). Multivariate logistic regression analysis demonstrated that pT (OR 2.5, 95%CI 1.61-3.82), presence of LVI (OR 2.7, 95%CI 1.24-6.14), negSLN (OR 0.59, 95%CI 0.39-0.88), and SLNMS (OR 2.8, 95%CI 1.74-4.63) were independent factors predicting non-SLN metastasis (Table 2).

Table 2. Multivariate logistic regression analysis for non-SLN metastasis

Factors	*OR*	*95% CI*	*p value*
Tumor size (pT)	2.5	1.61-3.82	<0.001
Lymphovascular invasion	2.7	1.24-6.14	0.013
SLN largest metastasis size	2.8	1.75-4.63	<0.001
Number of negative SLNs	0.59	0.39-0.88	0.01

SLN: sentinel lymph node, OR: odds ratio, CI: confidence interval

Table 3. Cumulative scores for 207 patients with and without non-SLN metastasis

Scores	*Total number of patients (%)*	*Number of patients without non-SLN metastasis (%)*	*Number of patients with non-SLN metastasis (%)*
0	6 (3)	6 (100)	0 (0)
1	7 (3)	7 (100)	0 (0)
2	4 (2)	4 (100)	0 (0)
3	31 (15)	30 (97)	1 (3)
4	20 (10)	18 (90)	2 (10)
5	40 (19)	35 (87)	5 (13)
6	30 (15)	22 (73)	8 (27)
7	20 (10)	5 (25)	15 (75)
8	19 (9)	4 (21)	15 (79)
9	19 (9)	6 (32)	13 (68)
10	11 (5)	0 (0)	11 (100)

Table 4. Number of patients and false negative rates at various scores by Ondokuz Mayis scoring system for 207 patients with 1-2 positive SLNs

Predictive risk scores (predicted probability)	*Number of patients* (%)*	*Number of patients with non-SLN metastasis (%)*	*False negative** rates %*
≤ 3 (≤ 5%)	48 (23)	1	2
≤ 4 (≤ 10%)	68 (33)	3	4.4
≤ 5 (≤ 15%)	108 (52)	8	7.4

* Number of patients with equal or lower than predicted risk scores (cut-off values).
**Estimated by the patients with non-SLN metastasis by the number of the patients.

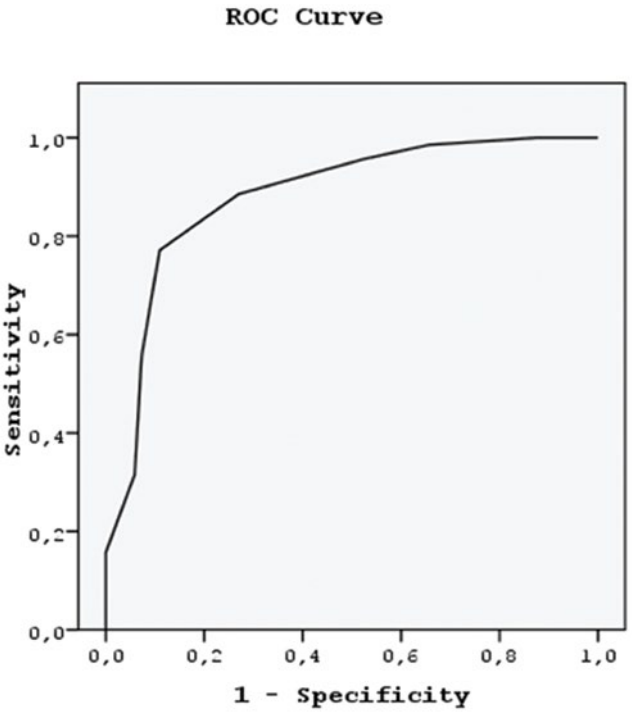

Figure 1. ROC curve and AUC for Ondokuz Mayis scoring system.

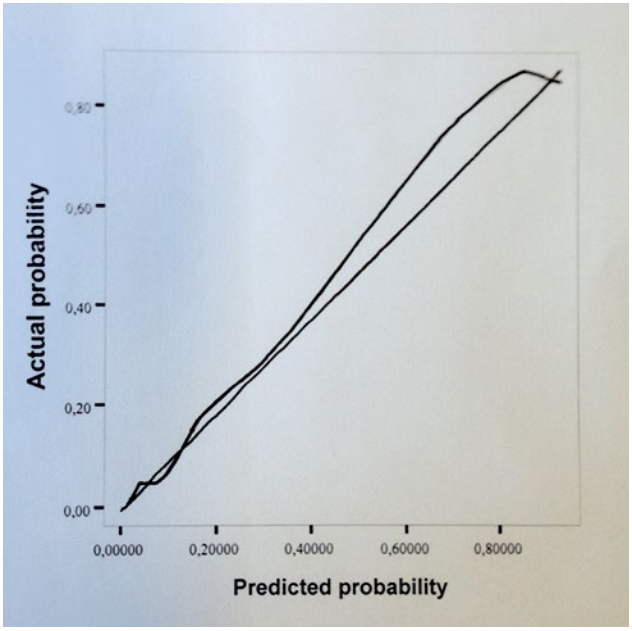

Figure 2. Calibration plot of Ondokuz Mayis scoring system.

The total number of patients with and without non-SLN metastasis by cumulative risk scores (0-10) is given in Table 3. There were 68 (33%) patients with score ≤ 4 (predicted probability of ≤10%) with a FNR of 4.4%. Thirty three patients with a score ≤ 4 could spare the ALND. One hundred and eight (52%) of 207 patients had a score of 5 (constituting the median score) or less. Among these patients, 8 had at least one metastatic non-SLN. With a score ≤5, the NPV was 92.6% and the FNR 7.4%. Patients with a predictive score of ≤ 5 had a 92.6% chance of having negative non-SLN metastasis, suggesting that they could be spared the axillary ALND (Table 4). To assess the clinical utility of the nomograms or scoring systems, FNR estimated at various scores or cut-off levels have been evaluated to define a subgroup of patients with a low predicted probability of non-SLN metastasis. The FNR and the proportion of patients with ≤3, ≤4, ≤5 scores and the matching cut-off levels of predicted probabilities of ≤5%, ≤10%, and ≤15%, respectively are shown in Table 4.

The generated ROC curve for the present series is presented in Figure 1. The calculated AUC value for the Ondokuz Mayis scoring system was 0.882 (95% CI 0.83-0.93). The sensitivity and specificity for the Ondokuz Mayis scoring system were 0.88 and 73%, respectively. The calibration plot for the Ondokuz Mayis model is presented in Figure 2. The Hosmer-Lemeshow goodness-of-fit test revealed that the p value was 0.23, suggesting a good calibration.

Discussion

Our findings demonstrate that the non-SLNs were negative in 66% of the patients with 1-2 metastatic SLNs. If the patients with 1-2 positive SLNs had been known to have negative non-SLNs, they would not have undergone ALND without any benefit for staging, outcome, or decision-making for adjuvant therapy. Furthermore, these patients would not have been exposed to the potential morbidity of ALND. The main problem is determining which patients with 1-2 posi-

tive SLNs should undergo completion ALND and which should not. To find a solution to this problem, predictive factors for non-SLN metastasis among patients with 1-2 positive SLNs have been investigated to predict the likelihood of non-SLN metastasis using predictive factors.

Our study revealed that tumor size, LVI, negSLN, and size of SLN metastasis (SLNMS) were the independent predictive factors associated with non-SLN metastasis in invasive T1-2 breast cancer patients with 1-2 metastatic SLN without ENE. These factors were used to create the present Ondokuz Mayis model. Tumor size, LVI, number of removed SLNs, negSLN, posSLN, pRatio, SLN metastasis size and grade have previously been found as predictive factors for positive non-SLNs in previous studies which investigated non-SLN metastasis in breast cancer patients with 1-2 SLNs [8-10]. Chen et al. [10] focused on the patients with 1-2 metastatic SLNs who might not fully match the Z011 criteria, and identified LVI, number of positive SLNs, and number of negative SLNs as independent factors associated with non-SLN metastasis. They created also the Shangai Cancer Center nomogram for prediction of non-SLN metastasis [10], and reported that the prevalence of non-SLNs metastases in their patient series was comparable to that in the ACOSOG trial (27%); only 24% of the patients had additional positive lymph nodes. The findings of the present study with 34% of non-SLN metastasis, however, contrast the study by Chen et al. [10] and the ACOSOG Z0011 [1]. In addition, although the size of SLN metastasis was significantly associated with non-SLN metastasis in univariate analysis, it was not a risk factor for non-SLN metastasis in multivariate analysis in that study. In fact the size of SLN metastasis was categorized as isolated tumor cells, micrometastasis and macrometastasis in the study by Chen et al. [10], whereas it was categorized as ≤ 2 mm, > 2-5 mm, > 5-10 mm, and > 10 mm in our study.

The present Ondokuz Mayis model has an excellent discrimination capacity, with an AUC of 0.88, and is higher than the AUC value of 0.78 presented by Chen et al. [10]. An AUC of 0.50 indicates no discrimination, 0.70 to 0.80 indicates acceptable discrimination, and 0.81 to 0.90 indicates excellent discrimination (AUC ≥ 0.90 is rare) [13]. Inspection of the calibration curve of our model and the Hosmer-Lemeshow test suggest that our model fits and was well-calibrated, and there were no significant difference between the predicted and the observed probabilities. Coutant et al. [14] and Mittendorf et al. [15] estimated the FN rates among patients with a score of ≤3.5 or a predictive probability of ≤10% for clinical utility. This is a useful choice for clinical use because the FN rate of SLN is usually accepted as <10% [16]. However, the predictive probability level of ≤15% has also been reported to be accepted as a definition of a subgroup with a low predicted probability of non-SLN metastasis to avoid ALND [10]. The definition of a subgroup with a low predicted value in the Ondokuz Mayis model showed that the FNR with a predicted score of ≤ 4 and ≤5 were 4.4% and 7.4%, respectively. Therefore, 68 (33%) or 108 (52%) patients at the predicted score cutt-off of ≤4 (predicted probability of ≤10%) or ≤5 (predicted probability of ≤15%), respectively, could have spared ALND in our series. In the Shangai Cancer Center non-SLN nomogram (SCC-NSLN) by Chen et al. [10], the FNR were 3.54% and 9.3% for the predicted probability cut-off points of ≤10% and ≤15%, respectively when applied to patients with 1-2 positive SLNs. Thus, 18% or 35% of the patients at the probability of non-SLN metastasis could spare ALND in their series. These findings showed that using Ondokuz Mayis scoring system ALND might be omitted in more patients than using SCC-NSLN.

In the study by Toshikawa et al. [9], 39% of 44 patients with 1-2 SLN metastases were found to have non-SLN metastasis which was associated with invasive tumor size and lymphatic involvement. Along with the small study size, the size of SLN metastasis had not been evaluated as a factor for non-SLN metastasis. In the present study, the size of SLN metastasis was a significant factor for non-SLN involvement. In another study from China, for ≤2 positive SLNs of breast cancer, the ratio of metastatic SLN/SLN and histological grading were found to be independent factors affecting non-SLN metastases [8]. The AUC of 0.62 (0.56-0.68) was below the acceptable discrimination. Therefore, the authors concluded that the results remained unsatisfactory for predicting the status of non-SLN [8].

The ACOSOG trial proved that among clinical T1-2 invasive breast cancer patients with 1-2 metastatic SLN and without ENE who underwent BCT, the SLNB-only arm had very low and similar axillary recurrrence rate compared with in the ALND arm [1]. However, as Chen et al. [10] reported that the findings of this trial should be taken cautiously due to the possible bias in patient selection. Patients in the ACOSOG Z0011 trial underwent BCT with whole-breast radiation, and therefore the generalization of these findings to mastectomized patients without radiotherapy is not certain [1]. Thus, predicting the factors for non-SLN metastasis in 1-2 SLN positive patients who are candidates for mastectomy is still im-

portant.

In the ACOSOG trial, the composition of the randomized groups to SLN-only and ALND arm were not equal, and the SLND-only arm had significantly more micrometastass compared with the ALND arm (p=0.02) [1]. Besides, the median tumor size, LVI, and macrometastasis rate were higher in our study. Therefore, the characteristics of patients in regard to micro-or macrometastasis rate, invasive tumor size, LVI in T1-2 invasive breast cancer with 1-2 SLN metastases were quite different in our study. Probably based on these characteristics, non-SLN metastasis was higher in our study (27 vs 34%). Considering these important differences, we are cautious in applying the ACOSOG trial in our patient group. We recommend the surgeons to know the characterstics of their patients before performing ALND in those that match the ACOSOG criteria.

The current scoring system is based on a relatively small sample size and has not been validated by another series. Almost all patients underwent simultaneous lumpectomy or mastectomy and frozen section SLN analysis in our clinic. Therefore, one of the predictive factors (LVI) was not available before the SLN analysis, and a second surgery for ALND might be required if the present model was to be used.

The present Ondokuz Mayis model with an AUC of 0.88 has an excellent discrimination capacity to distinguish patients at low risk for positive non-SLN from high risk patients. To the best of our knowledge, this is the only scoring system in a population which fully matches the ACOSOG Z0011 study [1]. Our model also was well-calibrated and our findings showed that the FNR with a predicted score of ≤4 (predicted probability of ≤10%) and ≤5 (predicted probability of ≤15%) were 4.4 and 7.4%, respectively. Therefore, 68 (33%) or 108 (52%) patients at the predicted score of ≤4 (predicted probability of ≤10%) or ≤5 (predicted probability of ≤15%) respectively could have been spared the ALND in our series. The calculation of scoring is simple by the independent factors used in this system and the application of Ondokuz Mayis scoring system is easy. For example, a patient with a tumor size of 2 cm, without LVI, with 2 negative SLNs and with 4 mm size of SLN metastasis would have a score of ≤4 with a predicted probability of ≤10%. ALND might be omitted in this patient, because the chance of a metastatic non-SLN would be as low as 4.4%.

Nomograms or scoring systems, which are methods to predict the possibility of non-SLN metastasis, do not yet have the ability to replace ALND, but they are increasingly being used by many surgeons [17]. As Scow et al. [18] noted, models always perform best in the population on which they are based. Thus, all nomograms and scoring systems may not have utility for all patient populations. Every clinic should validate a model before using it, or in the best case, every clinic should create a model, analyze it and consider the characteristics of the nomogram or scoring system in making decisions about omitting or performing ALND [19]. The characteristics of the nomogram or scoring system could also be shared with patients and their families during counseling before surgery.

Conflict of interests

The authors declare no confict of interests.

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