Original Article

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Associated Features with Non-Sentinel Lymph Node Involvement in Early Stage Breast Cancer Patients who Have Positive Macrometastatic Sentinel Lymph Node

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ABSTRACT

Objective: The main goal of this study is to determine the clinico-pathological factors that correlate non-sentinel lymph nodes (LNs) involvement in clinically node negative breast cancer (BC) patients with positive macrometastatic sentinel lymph node (SLN) in order to derive future evidence to define a subgroup where completion axillary lymph node dissection (cALND) might not be recommended.

Materials and Methods: Total 289 SLN biopsies were performed in clinically node negative BC patients between March 2014 and April 2017. Seventy patients who performed cALND due to positive macrometastatic SLN were retrospectively selected and classified into two groups, according to non-SLN involvement (NSLNI). Clinico-pathological features of patients were examined computerized and documentary archives.

Results: Extracapsular extension (ECE) of SLN, number of harvested SLNs, metastatic rate of SLNs, absence of ductal carcinoma in situ (DCIS) and presence of multilocalization were significantly associated with the likelihood of non-SLN involvement after univariate analysis ($p<0,05$). Absence of DCIS and presence of multilocalization were found to be significant after multivariate analysis.

Conclusion: Careful examination of clinico-pathological features can help to decide avoiding cALND if enough LNs are removed and the rate of SLN metastases is low, particularly in case DCIS accompanying invasive cancer in patients without multi localized tumour.

Keywords: Breast cancer, lymphatic metastasis, sentinel lymph node biopsy

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Introduction

The axillary nodal status is the most important prognostic factor in predicting the clinical outcomes in breast cancer (BC) patients. In recent years, sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) for an accurate staging and also to determine the prognosis and necessity of adjuvant therapies in BC patients with clinically negative axillary lymph nodes (1, 2). SLNB is a minimally invasive technique and safe, as well as lower morbidity compared with axillary dissection (2, 3). It is reported that the complication rates were, especially lymphedema, respectively 19.9% vs. 5.6% following ALND than SLNB during long-term follow-up (4).

When the sentinel lymph nodes (SLNs) are negative, ALND can be omitted due to the remaining axillary nodes were found free of disease (2). But it is still controversial to perform completion axillary lymph node dissection (cALND) in patients with SLN metastases (5). After the publishing ACASOG Z0011 and AMAROS studies, the importance of the non SLN involvement is considered less important (6, 7). However, cALND remains important for patients who have undergone mastectomy and cannot receive radiotherapy. After the IBCSG 23-01 study, the contribution of axillary dissection for micrometastatic lymph nodes to disease-free survival has not been demonstrated and there is still no standardization for axillary treatment (8). However, in most of the studies, while SLN positivity was identified, micro or macrometastasis was not differentiated (5, 6, 9). Therefore, knowing the specific factors affecting NSLNI in patients with macrometastasis in SLN may make a difference in approach to axilla. In terms of refraining from morbidity of ALND and also keeping in oncological safety, it is important to identify the related factors with additional nodal disease in BC with SLN macrometastasis.

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The main goal of this study is to determine the clinico-pathological factors that correlate non-sentinel lymph nodes involvement in clinically node negative BC patients with positive SLN in order to derive future evidence to define a subgroup where cALND might not be recommended.

Materials and Methods

The clinically early stage BC patients with the clinically axillary node negative, who underwent SLNB at Breast and Endocrine Surgery Unit of Ankara Numune Research and Training Hospital between March 2014 to April 2017, were reviewed as retrospectively from the our computerized and documentary archives. Informed consent was obtained from patients at the time of enrolment in the registry. Institutional ethical committee of Ankara Numune Research and Training Hospital approved the study (Number of ethics committee approval: E-17-1429).

Patients, who underwent to ALND due to positive SLN were taken into this study. The cases with receiving neoadjuvant chemotherapy, micrometastases in SLN, isolated tumour cells and more than 6 removed SLNs were excluded from the study. All patients carried out ultrasounds of both breast and axilla and the patients aged more than 40 years underwent to mammography (MMG) for the purpose of diagnosis and treatment planning. Patients were diagnosed as BC according to excisional & stereotactic biopsy, tru-cut biopsy and fine needle aspiration biopsy (FNAB) from suspicious breast mass. All the SLNB procedures were conducted via the use of blue dye such as patent blue, isosulfan blue and methylene blue. After the induction of anaesthesia, the blue dye was injected into the subareolar and perilesional areas in 10 mL volume and performed a massage to stimulate lymphatic drainage, for 10-12 minutes. Identified all blue nodes were accepted as SLNs and harvested. Pathologic evaluation of SLNs was performed with frozen section analysis intraoperatively, included sectioning at 2-mm intervals and staining with haematoxylin and eosin (H&E). If lymph nodes were negative with H&E, immunohistochemistry using cytokeratin antibody was performed. The determination of macrometastatic cells (>2 mm) within this period was described as a 'positive SLN' and further ALND was performed. Micrometastasis (0.2-2 mm), cell clusters and isolated tumour cells of <2 mm diameter were not accepted as a 'positive SLN' and so no more ALND performed.

Patient characteristics including age, side, localization and multilocalization of the tumour, presence of microcalcification on MMG, tumour characteristics including histological type, histological grade via the modified Bloom and Richardson system, tumour size, presence of lymphovascular invasion (LVI) and perineural invasion (PNI) and status of estrogen receptor (ER), progesterone receptor (PR), cerb-B2, p53, Ki67 and presence of DCIS accompanying invasive cancer, number of harvested SLNs and non-SLNs, SLN metastatic rate and extracapsular extension (ECE) of SLNs were assessed as possible estimated factors of axillary lymph node involvement. Multilocalization was defined as tumours that showed either or both multicentricity and multifocality. SLN metastatic rate was defined as the ratio of positive SLNs to total harvested SLNs.

After the final examination of enrolled surgical data and histopathological results, these patients with cALND were classified in two groups [(Group 1: non-sentinel lymph node involvement-, NSLNI (-) and Group 2: non-sentinel lymph node involvement, NSLNI (+).

Statistical analysis

The relationship between clinico-pathological variables and groups which was divided according to axillary lymph node involvement was initially evaluated using univariate analysis. Continuous data are presented as mean±SD while differences between groups were analysed by means of ANOVA test. Categorical variables were analysed with $\chi 2$ tests. Logistic regression was used to significant dependent variables associated with NSLNI. According to the number of risk factors which was independent variables, NSLNI rates was calculated by $\chi 2$ tests. A p-value less than 0.05 was considered statistically significant. All statistical tests were performed using IBM Statistical Package for the Social Sciences (IBM SPSS Corp.; Armonk, NY, USA), version 18.0, software.

Key Points

- cALND in breast cancer patients with positive SLN still remains important for patients who have undergone mastectomy and can not receive radiotherapy.
- In order to avoid overtreatment due to morbidity of ALND, it is crucial to identify the factors associated with NSLNI.
- However, the problem with the practical use of existing nomograms was that some parameters used, such as LVI or ECE of SLN, were not known during the operation.
- This study suggests that cALND is less necessary in breast cancer patients with positive SLN accompanied by DCIS but without multilocalization.

Results

SLN biopsies were performed in 289 clinically early stage BC patients. cALND were performed in 85 patients with positive SLN. Of these, 76 had macrometastases (26.3%), 8 had micrometastases (2.7%) and 1 (0.3%) had isolated tumour cells. And six other patients with more than 6 SLN excluded from the study. The remaining 70 patients were classified in two groups according to the involvement of non-SLN. A total of 32 patients in group 1 and 38 patients in group 2 were analysed. The age range was 21-80 years (mean: 51.4±12.8). There was no significant difference between groups in terms of age. We placed the diagnosis of malignancy with a tru-cut biopsy in 43 (62%) and with excisional & stereotactic biopsy in 27 (38%). SLND was applied to all patients with the use of blue dye. Three types of blue dyes were used. Patent blue in 53 (76%), isosulfan blue in 9 (13%) and methylene blue in 8 (11%). Multilocalization was seen in 11 (15.7%) of 70 patients and was found significantly associated with NSLNI (p=0.046). Forty-nine (70%) patients were underwent breast-conserving surgery that included lumpectomy and 21 (30%) modified radical mastectomy. The mean pathological tumour size was 2.400.98 cm. A total of 29 (41.42%) had a T1 tumor size while 41 (58.57%) patients with T2 tumor. The histological types of tumors were invasive ductal carcinoma (IDC) in 53 (76%), invasive lobular carcinoma (ILC) in 11 (16%), mixed invasive ductal and invasive lobular carcinoma in 3 (4%) and other in 3 (4%). Presence of DCIS accompanying invasive cancer histologically detected in 29 (41.4%), and absence of DCIS accompanying invasive cancer found statistically significant correlation with nodal involvement (p=0.021). Additional positive lymph nodes after ALND were identified in 38 of 70 (54.3%) patients with positive SLNs. The number of harvested SLN was minimum 1 and maximum 6 (mean: 2.921.42). SLN metastatic rate was 49% and 71.8% in group1 (NSLNI-) and group 2 (NSLNI+), respectively. ECE of SLNs was detected in 16 (22.8%) and all patients with ECE of SLNs were in group 2.

Clinicopathologic characteristics and results of the histopathological examination of the primary tumor and axillary lymph nodes are shown in Table 1 and Table 2.

ECE of SLNs (p<0.001), number of harvested SLNs (p=0.015), metastatic rate of SLNs (p=0.01), absence of DCIS accompanying invasive cancer (p=0.021) and multilocalization (p=0.046) were significantly associated with NSLNI on univariate analysis (p<0.05). These factors which were found to be significantly associated with NSLNI underwent to multivariate analysis. Multivariate analysis of potential risk factors showed that absence of DCIS accompanying invasive cancer (p=0.024) and presence of multilocalization (p=0.046) were independently associated with NSLNI in the present study (Table 3). If none, 1 or 2 of the risk factors is present, the estimated risks of NSLNI are found as 29.2%, 63.4% and 100 %, respectively (Table 4).

Discussion and Conclusion

Many studies investigated the different factors to predict the non-sentinel lymph node metastases in patients with positive SLN (5, 9). The present study revealed that ECE of SLNs, number of harvested SLNs, metastatic rate of SLNs, absence of DCIS and presence of multilocalization were significantly associated with the likelihood of NSLNI in BC patients on univariate analysis. Of these, only absence of DCIS accompanying invasive cancer and multilocalization were found to be independent factors that effect NSLNI. Presence of DCIS was negatively associated with NSLNI. This parameter has not been examined and reported as the independent predictor of NSLNI previously. But Ramjeesingh et al. (9) reported the negatively association of DCIS and SLN involvement and suggested that women with DCIS and small

Table 1. Patient characteristics associated with NSLNI

Characteristics	Group 1: NSLNI (-) n=32 (45.7%)	Group 2: NSLNI (+) n=38 (54.3%)	p
Age (mean±SD)	48.4±11	54.0±13.9	0.07
Tumor localization %, (n)			
Right	50% (16)	31.5% (12)	
Left	50% (16)	68.5% (26)	0.117
Multilocalization %, (n)			
No	93.7% (30)	76.3% (29)	
Yes	6.3% (2)	23.7% (9)	0.046
Microcalcification %, (n)			
No	65.6% (21)	68.4% (26)	
Yes	34.4% (11)	31.6% (12)	0.804
Number of harvested SLNs (mean±SD)	3.37±1.58	2.55±1.17	0.015
Number of harvested axillary nodes (mean±SD)	19.31±10.83	19.21±5.89	0.960
Number of total positive lymph node (mean±SD)	1.33±0.54	8.28±8.55	<0.01

NSLNI: non-sentinel lymph node involvement; MMG: mammography; SLN: sentinel lymph node

Table 2. Pathologic characteristics breast cancer patients

Characteristics	Group 1: NSLNI (-) n=32 (45.7%)	Group 2: NSLNI (+) n=38 (54.3%)	p
Tumour size (cm) (mean±SD)	2.32±0.75	2.46±1.15	0.549
DCIS %, (n)			
Absent	43.7% (14)	71% (27)	
Present	56.3% (18)	29% (11)	0.021
pT %, (n)			
T1	43.7% (14)	39.5% (15)	
T2	56.3% (18)	60.5% (23)	0.717
pN %, (n)			
N1	100% (32)	34.2% (13)	
N2	0% (0)	63.1% (24)	
N3	0% (0)	2.7% (1)	<0.001
HG %, (n)			
HG 1	28.1% (9)	18.4% (7)	
HG 2	40.6% (13)	50% (19)	
HG 3	31.3% (10)	31.6% (12)	0.591
ER %, (n)			
Negative	34.4% (11)	26.3% (10)	
Positive	65.6% (21)	73.7% (28)	0.464
PR %, (n)			
Negative	31.3% (10)	31.6% (12)	
Positive	68.7% (22)	68.4% (26)	0.591
Cerb-B2 %, (n)			
Score 1	78.1% (25)	71% (27)	
Score 2	6.3% (2)	10.6% (4)	
Score 3	15.6% (5)	18.4% (7)	0.753
Ki 67 %, (n)			
≤%15	31.3% (10)	15.7% (6)	
>%15	25% (8)	31.6% (12)	
Unknown	43.7% (14)	52.7% (20)	0,180
LVI %, (n)			
No	56.3% (18)	34.2% (13)	
Yes	43.7% (14)	65.8% (25)	0,064
PNI %, (n)			
No	87.5% (28)	71% (27)	
Yes	12.5% (4)	29% (11)	0,095
SLN metastatic rate (%)*	49.0	71.8	0.01
ECE of SLNs %, (n)			
No	100% (32)	57.9% (22)	
Yes	0% (0)	42.1% (16)	<0.001

*SLN metastatic rate =positive SLNs/ harvested SLNs. NSLNI: non-sentinel lymph node involvement; DCIS: ductal carcinoma in situ; ER: estrogen receptor; PR: progesterone receptor; Cerb-B2: epidermal growth factor receptor 2; LVI: lymphovascular invasion; PNI: perineural invasion; SLN: sentinel lymph node; ECE: extracapsular extension; HG: histologic grade.

Table 3. Multivariate analysis of clinical and pathological characteristics associated with NSLNI

Characteristic	Odds Ratio	95% CI	p
Presence of multilocalization	8.285	0.02-0.92	0.046
Absence of DCIS accompanying invasive cancer	5.464	0.042-0.802	0.024
Number of harvested SLNs	-	-	0.163
SLN metastatic rate (%)	-	-	0.781
ECE of SLNs	-	-	0.998

NSLNI: non-sentinel lymph node involvement; CI: confidence interval; DCIS: ductal carcinoma situ; SLN: sentinel lymph node; ECE: extracapsular extension.

Table 4. Correlation of risk factors (Presence of multilocalization and DCIS accompanying invasive cancer)

Number of risk factors	Group 1: NSLNI (-) (n=32, 45.7%)	Group 2: NSLNI (+) (n=38, 54.3%)	p
0	53.1% (17)	18.4% (7)	0.03
1	46.9% (15)	68.4% (26)	
2	0% (0)	13.2% (5)	

NSLNI: non-sentinel lymph node involvement; DCIS: ductal carcinoma situ

low-grade tumours may not require assessment of SLNs, intraoperatively. Another parameter that we examined was multilocalization. Multifocal/multicentric tumours are described as a presence of two or more discrete tumours in the same breast (in the same quadrant for multifocal tumours and different quadrants for multicentric tumours). As emphasized in the literature, multifocal/multicentric BCs have a higher rates of lymph node metastasis. Andea et al. (10) reported the relation between multifocality and axillary metastases. Similarly, we found multilocalization of the primary tumour as a predictor of NSLNI in the present study. Moreover 81.8% of patients with multilocality had additional axillary metastases. Although the number of patients in this study is low, if all independent predictive factors were present, 100% of cases with positive SLNs were found to have NSLNI+.

The relationship between tumour size and possibility of NSLNI has been reported in many studies. Ozmen et al. (11) found that tumour size larger than 2 cm was associated with higher risk of NSLNI. Also, Joseph et al. (12) demonstrated that primer tumour size was a predictor of NSLNI. The rates of metastatic non-SLNs were 0%, 12% and 47% for patients with T1a, T1b and T1c, respectively. But in the present study we could not find it as a statistically significant feature in both univariate and multivariate analysis. Similarly, Boler et al. (13), Abdessalam et al. (14) and Rahusen et al. (15) could not find an association between tumour size and NSLNI. High histological grade is another parameter that associated with an increased risk of NSLN (16, 17). But we could not find histological grade as a statistically significant predictive factor like previously demonstrated (18, 19).

Although many studies (14, 17) have reported similar results that LVI was enough to predict NSLNI, the univariate analyses revealed no significant differences between LVI and NSLNI in the current study.

Status of steroid receptors (particularly PR, not ER), Her-2 neu and Ki 67 mentioned as an independent predictive factors of axillary lymph node metastases previously (20). Also, we could not demonstrate any association between these parameters and NSLNI in our study.

Hwang et al. (18) reported that an increasing number of harvested SLNs is another parameter that associated with the likelihood of having additional lymph node metastases. Our study validated this association also. Number of positive SLNs and SLN metastatic rate (positive SLNs/ harvested SLNs) are the other demonstrated parameters that associated with NSLNI by two different studies (21, 22). The present study did not examine the number of positive SLNs as a predictor of NSLNI. But the univariate analyses revealed significant differences between two groups in terms of metastatic rate of SLN. Additionally, the significance rates were higher in patients with three or more harvested SLNs. However, the significance was lost in the multivariate analysis.

Size of the metastases in SLNs were usually defined as macrometastases (≤2 mm), micrometastases (≤2 mm) and isolated tumor cells (>2 mm) with the rates of non-SLN positivity, 48%, 23% and 12.5%, respectively (23). Due to the low metastatic rates, in our clinic we do not perform cALND in patients with micrometastases and isolated tumour cells in SLNs already. Therefore, these subjects were not studied in the present study. Besides size of the metastases, ECE of SLNs concerns us about the tumour cells in transit to other sites. ECE in SLN was demonstrated as a significant predictor of increased NSLNI for many times (24). In concordance with previous reports, in our study 100% of patients with ECE had NSLNI while 40.7% of patients without ECE were found to have additional axillary nodal metastases.

Based upon the most of clinicopathological features that mentioned above, many different nomograms have been developed, previously. In 2003, a nomogram by Van Zee et al. (22) from the Memorial Sloan Kettering Cancer Center (MSKCC) was published. This nomogram was based on eight parameters (type, size and grade of tumour, detection method of SLN, LVI, multifocality, ER status and SLN metastatic rate). Stanford model was reported in 2008, for predicting the NSLNI in SLN positive BC patients as another one, Cambridge model (25, 26). In fact, all of these nomograms were based on the synergistic interaction of these factors. But the problem in the practical use of nomograms was that some of the parameters used were not known during the operation such as LVI, ECE of SLN, ER status. Moreover, these nomograms based on the populations own features where they developed so they are in need to be validated in different patient populations. In different studies it was shown that Gur et al. (27) reported that the MSKCC nomogram, Cambridge Formula and Stanford nomogram were good discriminators for Turkish population, in their validation study. However, some other validation studies did not find nomograms reliable particularly for SLNs with micrometastatic involvement (28, 29).

The strengths of this study can be stated as follows. All the operations were applied by experienced surgeons of General Surgery Clinic, Breast and Endocrine Surgery Department. And pathological examinations were done by pathologists with the help of surgeons. Patients with neoadjuvant chemotherapy and more than 6 removed SLNs, who were thought to be able to influence the results of the statistical

analysis were excluded from the study. cALND was performed to all patients with a positive SLN.

On the other hand, the current study reflects the typical features of BC patients. The most important limitations of this study are, insufficient number of patients, the retrospective nature and detection method of SLN. We used only blue dye as a signing method of SLN. But also emphasized in the literature, both radioisotope and blue dye can be used to identify the SLNs in ESBC patients with the rate of 99% (30). With the use of the combined technique, the number of sentinel lymph nodes removed could be increased, which could affect the results in different ways.

In conclusion, this retrospective study demonstrated absence of DCIS accompanying invasive cancer as an independent predictor of NSLNI that has not mentioned in literature previously. Also, presence of multilocalization was found another important predictive factor of the lymph node metastasis. Careful examination of clinicopathologic features can help to decide avoiding cALND if enough lymph nodes are removed and the rate of SLN metastases is low, particularly in patients with presence of DCIS accompanying invasive cancer but without multilocalization. Finally, this study cannot be used to predict the NSLNI in daily clinical practice but may provide insight into new studies. Because there is still an ongoing argument on the predictive factors of axillary LN involvement. Future studies are needed to reveal more accurate subgroups of patients that might be avoided of axillary overtreatment in BC patients with SLN positive.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Numune Training and Research Hospital (Number of ethics committee approval: E-17-1429).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

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