Clinical and Experimental Health Sciences

Predictive Factors for Non-sentinel Lymph Node Metastasis of Breast Cancer

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ABSTRACT

Objective: The indications for axillary dissection after sentinel lymph node biopsy (SLNB) in breast cancer (BC) is gradually decreasing, even for selected patients with positive SLNB. Increased predictability of Non-sentinel lymph node (Non-SLN) metastasis could prevent unnecessary axillary dissection and even eliminate the need for SLNB. In this study we aimed to investigate the clinical and the pathological factors that affect Non-SLN metastasis.

Methods: Early breast cancer patients who underwent SLNB between 2013 and 2018 were retrospectively included in the study. Patients were divided into 3 groups; Group-1 SLNB negative patients, Group-2 SLNB positive but Non-SLN negative patients and Group-3 both SLNB and non-SLN positive patients. Groups were compared in terms of demographic data, tumor size, SLN size, Ki-67 percentages, and hormone receptor status.

Results: Seventy-six (36.4%) out of 206 patients had positive SLNB. Non-SLN metastases were detected in 33 (42.7%) patients. Mean tumor size found significantly higher in Group 3 (Group-1, 2 and 3 respectively; 20.5±9.7mm, 21.9±9.3mm, 25.1±9.5mm; p<.01). The mean SLN size was significantly bigger in Group-3 (Group-1, 2 and 3 respectively, 13.1±5.6mm, 13.9±8.2mm, 16.8±6.5mm; p<.01). Rate of patients with Ki-67 index higher than 14% was 84.3% in Group-3, 59.1% in Group-2 and 49.2% in Group-1(p<.01). A statistically significant difference was not detected between the groups in terms of hormone receptor status.

Conclusion: Tumor size, SLN size and Ki-67 percentages have importance in predicting the presence of Non-SLN metastasis in BC patients. These factors should also be taken into account for the management of the axillary metastasis and adjuvant treatment for BC.

Keywords: Breast cancer, Non-sentinel lymph node, Lymph node metastasis

1. INTRODUCTION

The assessment of lymph node metastasis is crucial for staging, prognosis and treatment of breast cancer (BC). In the 20th century, axillary lymph node dissection (ALND) was an irreplaceable part of breast cancer surgery. With the help of radiological improvements and screening programs, BC surgery has evolved from radical resections with axillary dissection to breast-conserving surgeries and SLNB's.

The increased risk of wound infections, seroma, axillary paresthesia, brachial plexus injury, and lymphedema causes surgeons to continue questioning the necessity of ALND [1]. Emerging studies on the idea have revealed that ALND can be avoided in a selected number of patients. Even though SLNB has become the standard practice in clinically node-negative patients, the requirement for axillary dissection has been decreasing. According to the ACOSOG Z0011 criteria axillary dissection can be averted even in the presence of metastatic sentinel nodes. The ACOSOG Z0011 randomized clinical trial showed no difference in 10-year overall survival between SLNB alone and ALND in T1 and T2 tumors with whole breast irradiation [2]. Studies comparing SLNB with ALND have shown that SLNB accurately identifies axillary metastases with less morbidity in patients with unifocal, node negative tumors less than 3 cm [3].

Nowadays the necessity of SLNB is a matter of discussion and predicting the presence of SLN and Non-SLN metastases in the axilla is important for planning the adjuvant treatment options for patients. The SLNB positivity is expected to be 30% in early stage BC patients. Only 30-40% of these patients

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present with Non-SLN metastasis [4,5,6]. As surgeons are moving further away from axillary dissections it is gaining importance to determine risk factors for Non-SLN metastasis. The purpose of this study was to investigate the risk factors for Non-SLN metastasis.

2. METHODS

2.1. Patient selection

Clinical and radiological node negative breast cancer patients who underwent breast-conserving surgery or mastectomy with SLNB at Istanbul Medeniyet University, Department of General Surgery between 2013 and 2018 were investigated retrospectively. Axillary dissection was performed routinely to all patients who had metastatic SLN after SLNB between 2013 and 2018 in our department. Patients who underwent neoadjuvant chemotherapy and patients with metastatic disease, multi-centric tumors, prior axillary surgery and per-operatively unidentified sentinel lymph node were excluded from the study. Two-hundred and six histologically confirmed invasive breast cancer patients, aged between 18 and 80 years, were included in the study. All patients provided written informed consent. The study was approved by the Ethics Committee of İstanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital (Approval date: 30.12.2014; Number: 2014/0200)

2.2. Sentinel lymph node biopsy

All participating patients underwent SLNB. Immediately after the induction of anesthesia 2-4 ml of methylene blue dye was injected to the subareolar area of the patients. Eight minutes after the injection of blue dye sentinel lymph nodes were excised through axillary incision. Frozen section examination was applied to all patients. The SLNs were then assessed intraoperatively via frozen section examination and subsequently cut into 2-mm serial sections for staining with standard hematoxylin and eosin. Presence of metastasis and size of the metastatic deposit was evaluated. Axillary dissection was performed in cases of macro-metastasis (metastasis ≥2mm) detected in sentinel lymph nodes.

2.3. Data Analysis

Patients were divided into three groups according to the pathological examination of their sentinel and non-sentinel lymph nodes. Group-1 consisted of patients with negative SLNB, Group-2 consisted of patients with positive SLNB results and negative Non-SLN. Group-3 consisted of patients with positive SLNB and positive Non-SLN. Patients' histopathological results of frozen sections, tumor and axillary dissection materials were reviewed. Tumor type, tumor size, SLN metastasis status, number of SLNs removed, SLN frozen section results, SLN paraffin-embedded section results, size of SLN, axillary dissection status, Non-SLN metastasis status, number of metastatic lymph nodes and total number of removed lymph nodes were assessed. For evaluating tumors according to Estrogen Receptor (ER), Progesterone Receptor (PR), Human epidermal growth factor receptor-2 (HER-2) and Ki-67 expressions, immunohistochemical analysis were performed for all patients. The Allred scoring system was used to evaluate ER and PR status [7]. Ki-67 percentages of each group were assessed according to the cut-off values of; 14% defined by 2011 St Gallen consensus and 20% suggested by majority of panelists of 2013 St Gallen consensus. Statistical analyses were performed comparing Ki-67 percentages by these cut-off values [8, 9].

2.4. Statistically Analysis

SPSS software version 20.0 (SPSS Inc., Chicago, IL) was used to analyze the data of this study. Descriptive statistics was applied in relevant parameters. Distributions of the numerical variables were examined by histograms and Shapiro–Wilk test. Where appropriate, comparisons of categorical variables were performed using the chi-squared test and continuous variables with median or mean values were compared using the Mann–Whitney U and Kruskal-Wallis tests. Spearman's rho correlation coefficient was used for the correlation analysis between the parameters. The results were reviewed in the confidence interval of 95%, and the value p< .05 was considered statistically significant.

3. RESULTS

Between 2013 and 2018 a total of 206 BC patients who underwent SLNB for clinically node negative breast cancer were included in the study. The patients' mean age was 55.4±12.5 years. Demographic data of the patients are shown in Table-1. Histologic subtypes of BC were invasive ductal carcinoma in 176−patients (85.4%), invasive lobular carcinoma in 15 patients (7.3%), papillary carcinoma in 9 patients (4.4%), and mucinous carcinoma in 6 patients (2.9%). SLNB results were negative for metastasis in 130 (63.1%) patients (Group-1) and positive for 76 patients. Out of 76 patients with positive SLNB's, 44 (21.4%) patients Non-SLN were negative (Group-2) and 32 (15.5%) patients Non-SLN were positive (Group-3). There was no significant difference between the groups in terms of age (Group-1: 55.2±12.7, Group-2: 56.6±14.1 and Group-3: 53.3±8.4 years, p= .322).

The mean tumor size of the patients was found to be 21.5±9.7 mm. We compared the tumor sizes of the groups, and it was found that the tumor sizes of the patients in Group-3 (25.1±9.5 mm) were significantly (p<.05) higher than the other groups (Group-1: 20.5±9.7mm; Group-2: 21.9±9.3 mm) (Table-1). Comparison of Group 2 and 3 according to tumor size also had statistically significant difference (p<.05) (Table-2).

The mean SLN size of patients was 13.8±6.4mm. The mean SLN size was 13.1±5.6mm in Group-1, 13.9±8.2mm in Group-2 and 16.8±6.5mm in Group-3. There was a statistically significant difference between groups in terms of SLN size (p<.05) (Table-1). When Group 2 and 3 were compared to determine the effect of lymph node size on

non-SLN metastasis, SLN size was statistically significantly higher in Group-3 (p<.05) (Table-2).

Table-1: *Demographic, clinical and histopathological data of patients with breast cancer.*

	Group-1 n=130	Group-2 n=44	Group-3 n=32	Total n=206	p value
	Mean±Sd	Mean±Sd	Mean±Sd	Mean±Sd	
Age[a]	55.2±12.7	56.6±14.1	53.3±8.4	55.4±12.5	.322
Tumor size (mm)[a]	20.5±9.7	21.9±9.3	25.1±9.5	21.5±9.7	**.003****
Ki-67 Proliferation Index[a]	19.2±20.4	19.4±17.3	22.2±12.3	19.7±18.7	**.017***
Sentinel lymph node size (mm)[a]	13.1±5.6	13.9±8.2	16.8±6.5	13.8±6.4	**.004****
	n(%)	n(%)	n(%)	n(%)	
Tumor side[b] – Right – Left	68 (52.3) 62 (47.7)	17 (38.6) 27 (61.4)	16 (50) 16 (50)	101 (49.1) 105 (50.9)	.290
Surgical technique[b] – Breast-conserving Surgery – Mastectomy	92 (70.8) 38 (29.2)	30 (68.2) 14 (31.8)	23 (71.9) 9 (28.1)	145 (70.4) 51 (29.6)	.929
Ki-67 Proliferation Index (%)[b] – >14% – <14%	64 (49.2) 66 (50.8)	26 (59.1) 18 (40.9)	27 (84.3) 5 (15.7)	116 (56.3) 90 (43.7)	**.001****
Lymphovascular invasion[a] – Positive – Negative	58 (44.6) 72 (55.4)	25 (56.8) 19 (43.2)	21 (65.6) 11 (34.4)	104 (50.5) 102 (49.5)	.661
Estrogen receptor status[b] – Positive – Negative	110 (84.6) 20 (15.4)	37 (84.1) 7 (15.9)	29 (90.2) 3 (9.8)	176 (85.4) 30 (14.6)	.514
Progesterone receptor status[b] – Positive – Negative	97 (74.6) 33 (25.4)	33 (75) 11 (25)	29 (90.2) 3 (9.8)	159 (77.2) 47 (22.8)	.143
HER-2 status[b] – Positive – Negative	41 (31.5) 89 (68.5)	12 (27.3) 32 (72.7)	8 (25) 24 (75)	61 (29.6) 145 (70.4)	.706
Triple negative patients	6 (4.6)	2 (4.5)	2 (6.7)	10 (4.9)	.944

[a] *Kruskal-Wallis test* [b] *Pearson Chi-square test *p<.05 **p<.01*

The Ki-67 percentages of the groups were 19.2±20.4 for Group-1, 19.4±17.3 for Group-2 and 22.2±12.3 for Group-3. The mean value of Ki-67 proliferation index was statistically significantly higher in Group-3 (p<.05). Groups were compared according to Ki-67 cut-off value of 14%. Out of 116 patients with Ki-67 results ≥ 14%, 64 (49.2%) had negative SLN (Group-1), 26 (59.1%) had positive SLNB (Group-2) and 27 (84.3%) had positive non-SLN (Group-3). The number of patients with Ki-67>14% was significantly higher in Group-3 (p<.001) (Table-1). When we compared Group-2 and Group-3 to evaluate the effect of Ki-67 proliferation index on Non-sentinel lymph node metastasis, we found a significant difference between these two groups. Group-3 had higher values in terms of both the mean Ki-67 and the number of patients with higher than 14% cut-off (Table-2).

Table-2: *Comparison of the histopathological factors between Group-2 and Group-3.*

	Group-2 n=44	Group-3 n=32	p value
	Mean±Sd	Mean±Sd	
Tumor size (mm)[a]	21.9±9.3	25.1±9.5	**.027***
Ki-67 Proliferation Index[a]	19.4±17.3	22.2±12.3	.062
Sentinel lymph node size (mm)[a]	13.9±8.2	16.8±6.5	**.018***
	n(%)	n(%)	
Ki-67 Proliferation Index (%)[b] – >14% – <14%	26 (59.1) 18 (40.9)	27 (84.3) 5 (15.7)	**.017***

[a] *Mann-Whitney U test* [b] *Pearson Chi-square test *p<.05 **p<.01*

Immunohistochemical analysis for the ER status of tumors revealed positive results for 110 (84.6%) patients in Group-1, 37 (84.1%) patients in Group-2 and 29 (90.2%) patients in Group-3. PR status for each group was determined positive in 97 (74.6%), 33 (75%) and 29 (90.2%) patients for Groups-1, 2 and 3, respectively. The number of patients with positive HER-2 expression was found 41 (31.5%) in Group-1, 12 (27.3%) in Group-2 and 8 (25%) in Group-3. Number of "triple negative (TN)" patients was 6 (4.6%) in Group-1, 2 (4.5%) in Group-2 and 2 (6.7%) in Group-3. Immunohistochemical analysis results did not show statistically significant difference between the groups (Table-1).

4. DISCUSSION

Axillary management of patients with newly diagnosed BC has undergone many practical changes in the last few decades with the impact of oncological treatment outcomes. Sentinel lymph node biopsy has replaced routine axillary lymph node dissection for the staging of clinically node-negative BC patients [10]. The presence and number of metastatic axillary lymph nodes are the most important factors that determine treatment options such as radiotherapy, axillary dissection and chemotherapy for BC patients. All BC patients with clinically negative axilla should be offered SLNB to provide information for node staging and relevant treatment decisions. According to ACOSOF Z0011 [11,12] and AMAROS [13] trials there are no difference in terms of survival in BC patients with proven 1 or 2 positive sentinel lymph nodes who underwent SLNB with whole breast irradiation and those who underwent ALND. American Society of Clinical Oncology clinical practice guideline [14] does not recommend ALND for early BC patients with one or two SLN metastasis who will undergo whole-breast radiotherapy. NSABP-B32 trial revealed no statistically significant differences between patients who underwent ALND and those who had SLNB in terms of overall survival, disease – free survival, and regional control [10].

Therefore, today axillary dissection can be abandoned in this selected patient group. Among these selected patients with SLN metastasis, only 40-60% have Non-SLN metastasis [14-16]. During their study, Mikami et al [17] observed Non-SLN metastasis in 35% of their patients with metastatic SLN. Our patient group had Non-SLN metastases in 32 (42.1%) of 76 patients with SLN metastasis which is consistent with the literature. Thus, more than half of the patients underwent ALND without a therapeutic benefit. All these results emphasize the importance of the predictability of metastases in non-SLN for the choice of treatment options in BC patients.

In light of the previous studies, today axillary dissection is not performed in selected patients with positive SLNB results. Therefore, we designed this study between 2013 and 2018, to investigate the results of patients who underwent axillary dissection because of positive SLNB results. Various studies have been conducted to predict the Non-SLN metastasis, most of them questioned scoring systems based on the number of metastatic SLN. Van la Parra et al [18] revealed that >1metastatic SLN, ≤1 non-metastatic SLN, the ratio of metastatic SLN >50%, tumor size, lymphovascular invasion, extra-capsular extension and size of metastatic lymph node were factors predicting presence of the Non-SLN metastasis. Maimaitiali et al [19] found that ≥3 metastatic SLN and lymphatic invasion were associated with Non-SLN metastasis. Mikami et al [17] showed in their study that patients who had ≥2 metastatic SLN, ≤1 non-metastatic SLN and >12% Ki-67 index significantly higher risk of Non-SLN metastasis.

Our study demonstrated that tumor size, SLN size, and Ki-67 proliferation index >14% were statistically significant to predict Non-SLN metastasis in early BC patients. Consistent with the previous studies, we did not detect any significant relation between the molecular subtypes and hormone receptor status and non-SLN metastasis.

Factors mentioned above have been assessed by various nomograms, but have not been able to generate a suitable nomogram to predict Non-SLN metastasis [20-25]. As the number of clinical studies to predict non-SLN metastasis increases, it will be possible to create nomograms with high accuracy.

In order to create a homogeneous cohort in our study, patients who had neoadjuvant chemotherapy, metastatic disease, multi-centric tumors, or prior axillary surgery excluded from the study. This study has some limitations such as small number of cases and its retrospective nature.

5. CONCLUSION

Tumor size, SLN size and Ki-67 proliferation index higher than 14% are seen as significant factors in predicting Non-SLN metastasis in early-stage BC patients. In light of our study we advise the use of these factors together with the criteria defined by previous studies to diagnose Non-SLN metastasis. These factors should also be taken into account during the axillary management and adjuvant treatment for BC.

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