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Sentinel Node Ratio as a Predictor of Non-sentinel Lymph Node Involvement

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ABSTRACT

Background: Sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) in early breast cancer patients as the first line surgical approach to axillary nodes. Further dissection is performed only when SLN is involved by tumor cells. However, in a significant proportion of patients, non-sentinel nodes are still not involved and axillary dissection has no additional therapeutic benefits. Selective axillary clearance has been considered to prevent unnecessary dissection. The purpose of this study was to define predictors of non-sentinel lymph node involvement in patients with positive SLNB.

Methods: Patients with early stage breast cancer and positive SLNB who underwent ALNDin a referral hospital in Tehran, Iran between2010 and 2012 were recruited into the study. Relations between different clinico-pathological characteristics and involvement of non-sentinel nodes were investigated.

Results: From 139 patients who had positive SLNB and underwent ALND, only in 71 cases (51%) positive non-sentinel lymph nodes (NSLNs) were detected. In univariate analysis, there was no association between tumor size, lymphovascular invasion, ER, PR and HER-2 expression and NSLN metastasis. In contrast, presence of more than one SLN ($P = 0.016$) and a sentinel node ratio (SNR) more than 0.5 showed a significant association ($P< 0.001$). Only the latter remained as the significant predictor of NSLN involvement in mutltivariate analysis ($P < 0.001$, OR = 3.706).

Conclusions: Based on our results, patients with a SNR more than 0.5 were more commonly diagnosed with NSLN metastasis. Thus, it is recommended that surgeons think twice before skipping ALND in this subgroup of patients.

Introduction

For about a century, axillary lymph node dissection (ALND) was performed routinely in all breast cancer patients for staging and management of probable axillary lymph node metastasis by removing most of the axillary nodes. However, a considerable proportion of patients had no axillary involvement and did not benefit from axillary dissection. Significant morbidity associated with ALND along with high rate of negative dissections lead to introduction of sentinel lymph node biopsy (SLNB) as a modification of standard surgical care for breast cancer. [1]

In early nineties, SLNB was introduced by Krag *et al*. and Giuliano *et al*. for patients with early

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stage breast cancer.[2,3] Numerous trials have confirmed the accuracy of this method with low false negative results.[4,5] Axillary recurrence rate in case of negative SLNB has reported to be as low as one percent.[4] It is widely suggested that in case of positive SLNB, patients proceed to standard ALND. However, recent trials have doubted the advantage of ALND following positive SLNB in all patients.[6,7]

Even in the SLNB era, the problem of unnecessary ALND exists. As in case of SLN involvement where in a significant proportion of patients, axillary dissections yield no additional positive lymph node(s).[8,9] A significantly increased rate of unnecessary ALND following positive SLNB resulted in proposing a selective approach to performing ALND.[10,11] This study was conducted to assess predictive factors associated with positive non-sentinel lymph nodes (NSLNs) in patients with early stage breast cancer who had a positive SLN.

Methods

In a prospectivestudy, 139 consecutive women with early stageinvasive breast cancer were recruited. All enrolled patients were at least 18 years old with no clinical evidence of axillary involvement and at least one positive node in SNLB. Pathological assessment of SLN was performed by frozen section and only macrometastases were detected. All operations were performed in a teaching hospital affiliated with Tehran University of Medical Sciences between April 2010 and December 2012 in Tehran, Iran.

All patients underwent ALND following positive SLNB. Based on tumor size, breast size and patients' preference, the type of surgery was either breast conserving surgery (BCS) or modified radical mastectomy (MRM). Patients received radiotherapy, chemotherapy or hormone therapy following surgery based on stage of the disease and receptor expression.

Size, histologic and nuclear grade of tumor, presence of lymphovascular invasion and number of total harvested sentinel lymph nodes and positive nodes were obtained from histopathologic reports of breast and dissected axillary tissues. Immunohistochemistry (IHC) staining of breast tissue was performed to determine expression of estrogen receptor (ER), progesterone receptor (PR) and HER2 in primary tumors. Sentinel node ratio (SNR) was defined as the number of positive SLNs divided to total resected SLNs.

Table1. Baseline characteristics of enrolled patients

	Total (N = 139)	Negative NSLN (N = 68)	Positive NSLN (N = 71)
Mean age (year)	47.8 ±11.5	46.6 ± 10.1	48.9 ± 12.7
Mean tumor size (cm)	2.8 ± 1.5	2.5 ± 1.2	3.1 ± 1.7
Pathology			
IDC	132 (94.9%)	65 (96.6%)	67 (94.4%)
ILC	7 (5.1%)	3 (3.4%)	4 (5.6%)
Tumor size			
⩽ 2cm	52 (37.4%)	28 (41.1%)	24 (33.8%)
> 2cm	78 (56.1%)	35 (51.5%)	43 (60.6%)
Unknown	9 (6.5%)	5 (7.4%)	4 (5.6%)
Histologic grade			
I and II	95 (68.4%)	42 (61.7%)	53 (74.6%)
III	22 (15.8%)	11 (16.2%)	11 (15.5%)
Unknown	22 (15.8%)	15 (22.1%)	7 (9.9%)
Lymphovascular invasion			
Yes	77 (55.3%)	31 (45.6%)	46 (64.8%)
No	39 (28.1%)	20 (29.4%)	19 (26.7%)
Unknown	23 (16.6%)	17 (25.0%)	6 (8.5%)
Receptor status			
ER +	105 (75.5%)	47 (69.1%)	58 (81.7%)
PR +	92 (66.1%)	40 (58.8%)	52 (73.2%)
HER2 +	41 (29.4%)	20 (29.4%)	21 (29.6%)
SNR			
⩽ 0.5	56 (40.3%)	39 (57.4%)	17 (23.9%)
> 0.5	83 (59.7%)	29 (42.6%)	54 (76.1%)
Number of positive SLNs			
1	86 (61.9%)	49 (72.1%)	37 (52.1%)
> 1	53 (38.1%)	19 (27.9%)	34 (47.9%)

Abbreviation: NSLN; Non-sentinel lymph node biopsy, IDC; Invasive ductal carcinoma, ILC; Invasive lobular carcinoma, SNR; Sentinel node ratio.

Associations between demographic and histopathological characteristics with involvement of NSLNs were investigated using Chi-Square test. Variables that showed a significant association in univariate analysis were put in a logistic regression model to identify independent predictors. Data was analyzed by SPSS software version 20.0 (IBM, NY, USA). P value less than 0.05 was considered as statistically significant.

Results

A total of 139 patients with a mean age of 47.8±11.5 years were enrolled in the study. Invasive ductal carcinoma (IDC) was the most frequent pathological type of tumor detected in 94.9% of study subjects. Demographic and histopathological characteristics are demonstrated in table 1. NSLN was positive in 71(51%) participants. Median number of dissected SLNs and NSLNs were 2 (ranging from 1 to 12) and 10 (ranging from 1 to 20), respectively.

Univariate analysis demonstrated that most of the patients in both groups (positive and negative NSLN) had tumors larger than 2 cm (60.6% vs. 51.5%), with no significant differences between the groups (P = 0.316). Histologic grade III was only reported in 15.5% and 16.2% of subjects with positive and negative NSLN, respectively (P = 0.779). There were no statistical differences between the two groups regarding lymphovascular invasion (P = 0.260), ER (P = 0.165), PR (P = 0.133) and HER2 (P = 0.482) expressions.

Patients with more than one positive SLN were more likely to have positive NSLN (47.9% vs 27.9%, P = 0.016). Also, SNR more than 0.5 was associated with a higher rate of positive ALND (76.1% vs 42.6%, P< 0.001). In multivariate analysis of the two predicting factors, only SNR more than 0.5 had an independent significant predicting role(P = 0.001, OR = 3.706) (Table 3).

Table 2. Assessing the predictive role of tumor characteristics for non-sentinel axillary node Metastases

	Univariate analysis	
	Odds Ratio (95% CI)	P-value
Lymphovascular invasion	1.562 (0.719 – 3.393)	0.260
Nuclear grade 3	2.111 (0.882 – 5.052)	0.093
Tumor size > 2cm	1.433 (0.709 – 2.899)	0.316
Histologic grade III	1.112 (0.530 – 20.33)	0.779
ER +	1.920 (0.764 – 4.824)	0.165
PR +	1.820 (0.834 – 3.972)	0.133
HER2 +	0.906 (0.687 – 1.194)	0.482
Sentinel node ratio > 0.5	4.272 (2.065 – 8.835)	<0.001
Positive sentinel nodes >1	2.370 (1.171 – 4.797)	0.016

Table 3. Multivariate analysis of factors that showed significant association in univariate analysis for predicting NSLN metastasis

	Odds ratio	P-value	Confidence Interval	
			Lower	Upper
Sentinel node ratio > 0.5	3.706	0.001	7.934	7.934
Positive sentinel nodes > 1	1.582	0.241	3.402	3.402

Discussion

The recent trend in breast cancer management is towards more conservative approaches, while the disease-free and overall survival rates of patients are not diminished. In this regard, BCS has replaced the more invasive surgical approaches such as radical mastectomy or MRM in most patients. Considering the importance of axillary lymphatic drainage as the most common site of breast cancer metastasis, there has been extensive debate on the therapeutic approach toward axillary involvement.[12] SLNB has replaced ALND as the first line surgical technique for assessment of axillary nodes, but performing complete ALND after positive SLNB remains controversial.[13]

In the current study, our aim was to identify predictive factors of NSLN metastases. Women with early stage breast cancer who had SLN involvement were proceeded to ALND but only in half of them NSLN involvement was identified.

Metastasis to more than one SLN and SNR were the only factors that showed significant association in univariate analysis. In binary logistic regression model, only the latter remained as the independent predictor of NSLN tumoral involvement.

There were several reports indicating predictive role of age, tumor size, and lymphovascular invasion regarding positive SLNB, but similar findings were not reported for further axillary metastasis.[14-16] On the contrary, histopathologic evaluation of SLN was more promising in anticipating the NSLN metastasis compared to features of the primary tumor.[16] The features of SLN which have been shown to be predictive include number of positive SLNs, size of SLN metastasis, and presence of extracapsular invasion in positive nodes.

While involvement of NSLN cannot be accurately predicted based on the size of the primary tumor, it has been suggested that patients with larger involved SLNs are prone to further axillary metastasis.[9,17] Those with macrometastasis in SLNB were at higher risk of axillary involvement compared to patients with isolated tumor cell (ITC) or micrometastasis.[16] A potential weakness of the current study was the lack of data on patients who had ITC or micrometastasis, as only patients with macrometastasis in frozen section were included.

The other factor which has been shown to be associated with NSLN metastasis is the number of positive nodes in SLNB. Wong *et al.* and Chu *et al.* have both demonstrated that patients with more than one positive SLN have a risk of NSLN involvement as high as 50%, in comparison to those with only one positive SLN who had a 30% risk of further lymphatic metastasis[18,19]. In the present study, consistent with published literature, patients with more than one positive SLN encountered NSLN metastasis more frequently. The corresponding figures in patients with more than one or only one positive SLN were 64.1% and 43.0% in our study participants, respectively.

Previous results of studies on the predictive role of lymphovascular invasion in the primary tumor are inconsistent.[19,20] While several researchers could not detect an association, others have implicated lymphovascular invasion as an independent predicting factor.[21] Our observation failed to demonstrate a significant association between lymphovascular invasion and NSLN metastasis.

Previously, two breast cancer nomograms for predicting NSLN involvement have suggested that SNR can be an important factor associated with metastasis to NSLN.[21,22] Dividing the number of positive nodes to total harvested nodes was previously used for axillary lymph nodes to obtain the lymph node ratio (LNR). LNR has been suggested as an important prognostic factor for predicting patients' survival.[23,24] Based on the recent investigations and the results of the current study, it seems that SNR has an important clinical value as well.

In conclusion, patients with more than one positive node in SLNB and a SNR more than 0.5 might be at increased risk of NSLN involvement and should be considered for assessment of axillary nodes.

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