

## RESEARCH ARTICLE

# Clinicopathologic Features Predicting Involvement of Non-sentinel Axillary Lymph Nodes in Iranian Women with Breast Cancer

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### Abstract

**Background:** Almost half of the breast cancer patients with positive sentinel lymph nodes have no additional disease in the remaining axillary lymph nodes. This group of patients do not benefit from complete axillary lymph node dissection. This study was designed to assess the clinicopathologic factors that predict non-sentinel lymph node metastasis in Iranian breast cancer patients with positive sentinel lymph nodes. **Materials and Methods:** The records of patients who underwent sentinel lymph node biopsy, between 2003 and 2012, were reviewed. Patients with at least one positive sentinel lymph node who underwent completion axillary lymph node dissection were enrolled in the present study. Demographic and clinicopathologic characteristics including age, primary tumor size, histological and nuclear grade, lymphovascular invasion, perineural invasion, extracapsular invasion, and number of harvested lymph nodes, were evaluated. **Results:** The data of 167 patients were analyzed. A total of 92 (55.1%) had non-sentinel lymph node metastasis. Univariate analysis of data revealed that age, primary tumor size, histological grade, lymphovascular invasion, perineural invasion, extracapsular invasion, and the number of positive sentinel lymph nodes to the total number of harvested sentinel lymph nodes ratio, were associated with non-sentinel lymph node metastasis. After logistic regression analysis, age (OR=0.13; 95% CI, 0.02-0.8), primary tumor size (OR=7.7; 95% CI, 1.4-42.2), lymphovascular invasion (OR=19.4; 95% CI, 1.4-268.6), extracapsular invasion (OR=13.3; 95% CI, 2.3-76), and the number of positive sentinel lymph nodes to the total number of harvested sentinel lymph nodes ratio (OR=20.2; 95% CI, 3.4-121.9), were significantly associated with non-sentinel lymph node metastasis. **Conclusions:** According to this study, age, primary tumor size, lymphovascular invasion, extracapsular invasion, and the ratio of positive sentinel lymph nodes to the total number of harvested sentinel lymph nodes, were found to be independent predictors of non-sentinel lymph node metastasis.

**Keywords:** Breast cancer - sentinel node biopsy - non-sentinel node metastasis - predictors

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### Introduction

Axillary lymph node (ALN) status is an important factor in the staging, prognosis and selection of an appropriate treatment modality in early breast cancer. Axillary dissection is currently the standard of care in patients with a positive sentinel lymph node (SLN) (McMasters et al., 2000; Cady, 2001). Recently, the survival benefit of completion axillary lymph node dissection (ALND) for all patients with a positive SLN has been questioned (Giuliano et al., 2011). Some studies have indicated that non-sentinel lymph node (NSLN) metastasis was observed in only 35% to 50% of breast cancer patients with a positive SLN (Chu et al., 1999; Turner et al., 2000). Therefore, 50% to 65% of patients with a positive SLN suffer from the morbidity of unnecessary ALND, such as

hand paresthesia, shoulder dysfunction and lymphedema (Schrenk et al., 2000; Lucci et al., 2007; Ashikaga et al., 2010). Nowadays, there is an increased tendency to avoid completion ALND in selected patients with a positive SLN (Noguchi, 2008).

Many studies have identified factors including tumor size, histological type, nuclear and histological grade, lymphovascular invasion (LVI), estrogen and progesterone receptor (ER and PR) status, and HER-2/neu expression, as predictors of NSLN metastasis (NSLNM) in patients with a positive SLN (Yu et al., 2005; Ozmen et al., 2006; Wada et al., 2006; Kapur et al., 2007; Boler et al., 2012; Eldweny et al., 2012). These factors have been used to develop nomograms to predict the risk of NSLNM (Van Zee et al., 2003; Barranger et al., 2005; Kohrt et al., 2008; Pal et al., 2008). The validity and accuracy of

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clinicopathologic factors to predict NSLNM were different in various studies. A meta-analysis performed by Van la Parra et al. in the Netherlands, analyzed the results of 56 studies on predictive factors published between January 1999 and June 2009. Among all the variables which had a significant association with NSLNM in individual studies, only eight characteristics were found to have the highest likelihood to predict NSLNM (Van La Parra et al., 2011).

In spite of the numerous studies, it is still not yet clear whether a subgroup of patients with a positive SLN can be safely spared completion ALND. The purpose of this study was to define the clinicopathologic features of the primary tumor and SLN associated with NSLNM in patients with a positive SLN in a cancer referral center in Iran.

### Materials and Methods

We reviewed the medical records and pathology reports of patients who had undergone a SLN biopsy in Cancer Institute, Tehran University of Medical Sciences, between 2003 and 2012. The patients who had at least one positive SLN and underwent completion ALND were enrolled in the present study. The inclusion criteria were

the presence of micro or macrometastasis, or isolated tumor cells (ITCs) in the SLN. Patients who received neo-adjuvant chemotherapy were excluded from the study.

SLN biopsies were performed using blue dye method, radiocolloide injection, or a combination of both methods, by surgeons trained for SLNB. The detection methods of SLN metastasis were frozen sectioning during the operation and standard staining of paraffin sections.

Primary tumor size was classified as T1 ( $\leq 20$ mm), T2 ( $20 < \text{size} \leq 50$ mm), and T3 ( $> 50$ mm) (Singletary et al., 2002). The size of the SLN metastasis was categorized according to the American Joint Committee on Cancer (AJCC) in the sixth edition of the Cancer Staging Manual. Lymph node metastatic lesions with a maximum diameter of  $\geq 2$ mm were defined as macrometastasis (pN1), lesions with a diameter of 0.2-2mm as micrometastasis (pNmi), and a lesion of single tumor cells, or small cell clusters with a diameter  $< 0.2$ mm were defined as ITCs [pN0(i+)] (Singletary and Greene, 2003). Histological and nuclear grade based on a modified Scarff-Bloom & Richardson score were divided into three grades.

Pathology reports and the original hematoxylin and eosin (H&E) slides were reviewed for histological size

**Table 1. Univariate and Multivariate Analysis of Association of Clinicopathological Characteristics with Non-sentinel Lymph Node Metastasis.**

Variable	Non sentinel lymph node			P-Value	Crude OR	Odds Ratio (95% CI)	
	Negative NSLN(75)	Positive NSLN(92)	P-Value			Adjusted OR	P-value
Age	<40	14 (35.9%)	25 (64.1%)	0.001	Reference	Reference	
	$\geq 40$	61 (48.4%)	65 (51.6%)		0.6 (0.3-1.3)	0.13 (0.02-0.8)	0.03
Histological tumor size(mm)	T1 (size $\leq 20$ )	26 (72.2%)	10 (27.8%)		Reference	Reference	
	T2 (20< size $\leq 50$ )	47 (40.9%)	68 (59.1%)	0.001	3.1( 1.5-6.6)	7.7(1.4-42.2)	0.02
	T3 (size $> 50$ )	-	11 (100%)		---	---	
Multifocality	NO	67 (49.2%)	69 (50.8%)	0.06	Reference	Reference	0.2
	YES	8 (29.6%)	19(70.4%)		1.9 (0.8-4.9)	0.2 (0.02-1.9)	
Tumor histology	Ductal	68 (44.7%)	84 (55.3%)	0.4	---	---	---
	Lobular	5 (55.5%)	4 (44.5%)		---	---	---
	Mixed	1(25%)	4 (75%)		---	---	---
	other	1(1.3%)	---		---	---	---
Nuclear grade	Grade 1	8 (57.1%)	6 (42.9%)	0.2	Reference	Reference	
	Grade 2	51(45.9%)	60(54.1%)		1.1 (0.3-3.7)	0.3 (0.02-2.9)	0.3
	Grade 3	9(30%)	21 (70%)		2.1 (0.5-8.4)	0.1 (0.004-1.2)	0.1
Histological grade	Grade 1	15 (65.2%)	8(34.8%)	0.02	Reference	Reference	
	Grade 2	46 (42.6%)	62 (57.4%)		2 (0.7-5.2)	2.1 (0.4-11.4)	0.4
	Grade 3	6 (26%)	17 (74%)		3.8 (1.01-13.8)	5.5 (0.3-91.8)	0.2
Estrogen Receptor	NO	14 (42.4%)	19(57.6%)	0.7	---	---	---
	YES	53 (45.7%)	63 (54.3%)		---	---	---
Progesterone Receptor	NO	17 (37%)	29(63%)	0.2	Reference	Reference	
	YES	50 (48.5%)	53 (51.5%)		0.6 (0.3-1.2)	1.7(0.3-9.6)	0.6
Her-2/ neu	NO	44 (42.7%)	59 (57.3%)	0.3	---	---	---
	YES	23 (51%)	22 (49%)		---	---	---
P53	NO	23(36.5%)	40(63.5%)	0.2	Reference	Reference	
	YES	23(47%)	26(53%)		0.7 (0.3-1.4)	0.7(0.2-3)	0.9
Lymphovascular invasion	NO	22 (78.6%)	6(21.4%)	0.001	Reference	Reference	
	YES	51(38%)	83 (62%)		4.8 (1.8-13)	19.4(1.4-268.6)	0.03
Preineural invasion	NO	53 (56.4%)	41 (43.6%)	0.001	Reference	Reference	
	YSE	18 (29.5%)	43 (70.5%)		2.5 (1.2-5)	0.8 (0.2-3.4)	0.7
Type of diagnosis	Frozen	62(43.3%)	81 (56.7%)	0.4	---	---	---
	Standard paraffin	11 (52.4%)	10 (47.6%)		---	---	---
Size of SLN metastasis	Macrometastasis	61(42%)	84(58%)	0.1	Reference	Reference	
	Micrometastasis	9(64.3%)	5(35.7%)		0.4(0.1-1.3)	1.7(0.1-20.7)	0.7
Extracapsular invasion	NO	51 (57.3%)	38 (42.7%)	0.001	Reference	Reference	
	YES	15 (25.4%)	44 (74.6%)		3.1 (1.5-6.6)	13.3(2.3-76)	0.004
Number of positive SLN	1	54(47.4%)	60(52.6%)	0.3	---	---	---
	$> 1$	21(39.6%)	32(0.6%)		---	---	---
PSLN/TSLN ratio	$< 100\%$	49(62.8%)	29(37.2%)	0.0001	Reference	Reference	
	100%	26(29.2%)	63(70.8%)		4.1 (2.1-7.8)	20.2(3.4-121.9)	0.001

and multifocality of the primary tumor, LVI and perineural invasion (PNI) in the area of the primary tumor, nuclear and histological grade, histological type of tumor, detection method of SLN metastasis, size of SLN metastasis (micro or macrometastasis), extracapsular invasion (ECI) in the SLN, number of harvested and positive SLNs, and NSLNs. The ER, PR and P53 status, and HER-2/neu expression were extracted from the patients' medical records.

We studied the association of NSLNM, as an outcome in patients with positive SLN, with age, histological size, multifocality, histological type of the primary tumor, LVI, PNI, ER, PR and P53 status, HER2/neu expression, nuclear grade, histological grade, detection method of SLN metastasis, ECI, number of positive SLNs, number of positive SLNs to the total number of harvested SLNs (PSLNs/TSLNs) ratio, and the size of the SLN metastasis. We used a logistic regression model to estimate odds ratio (OR) and corresponding 95% confidence interval (95% CI). Results of the crude and adjusted regression model were presented. Factors significantly related to NSLNM in patients with a positive SLN with a p-value of 0.2 or less were entered into a backward stepwise multiple logistic regression model. We carried out a Co-linearity test between variables to control co-variability between the variables and thus identify independent predictors for the NSLNM in patients with a positive SLN. In addition, we excluded variables with a p-value of more than 0.2 from the model, although we presented the crude ORs for all putative risk factors. We used Stata statistical software (version 11) to perform the statistical analyses. The Regional Ethics Committee of Tehran University of Medical Sciences approved this study.

## Results

The files and pathology reports of 607 patients who underwent a SLN biopsy between 2003 and 2012 were reviewed. Data of 167 female breast cancer patients who had a positive SLN on frozen or permanent pathology were analyzed. The mean age of the patients were 47.4 ( $\pm 10.7$ ) years. The average number of harvested SLNs was 2.3 ( $\pm 1.4$ ) and the average number of positive SLNs was 1.5 ( $\pm 0.95$ ). Ninety two patients (55.1%) had NSLNM. The average number of harvested NSLNs was 9.9 ( $\pm 4.1$ ) and the average number of positive NSLNs was 2.3 ( $\pm 3.2$ ).

Univariate analysis revealed that age, histological tumor size, multifocality, nuclear grade, histological grade, PR and P53 status, LVI, PNI, size of SLN metastasis, ECI and PSLNs/TSLNs ratio, were significantly associated with NSLNM in patients with positive SLN (Table 1). However, in the multivariate logistic regression age, LVI, ECI, primary tumor size, and PSLNs/TSLNs ratio, remained significant predictors of NSLNM. Patients who were over 40 years had an 87% lower risk of NSLNM compared to those who were younger than 40 years (OR=0.13; 95% CI, 0.02-0.8). The risk of NSLNM was 19-fold higher in patients with LVI (OR=19.4; 95% CI, 1.4-268.6). In addition, patients with ECI had a 13-fold higher risk of NSLNM compared to those without ECI (OR=13.3; 95% CI, 2.3-76). Moreover, patients with histological size of the primary tumor between 20 and 50mm had a higher

risk of NSLNM compared to patients with a tumor size less than 20mm (OR=7.7; 95% CI, 1.4-42.2). The risk of NSLNM in patients with a PSLNs/TSLNs ratio of 100% was 20-fold higher compared to patients with a ratio of less than 100% (OR=20.2; 95% CI, 3.4-121.9) (Table 1).

## Discussion

Recently, the role of ALND as a standard of care in patients with positive SLN has been questioned. Almost 50% of breast cancer patients with a positive SLN who undergo ALND have no additional disease in NSLNs and this subset of patients do not benefit from this intervention. There are also some reports of the low incidence of regional failure in patients with SLN metastasis who did not undergo ALND because of associated comorbidity or patient refusal (Fant et al., 2003; Guenther et al., 2003; Jeruss et al., 2005).

Based on these observations, numerous studies have been performed to determine the predictive factors of NSLNM involvement in patients with SLN metastasis in order to identify a subset of patients who can be spared a negative ALND safely.

The relationship of age to the prognosis of breast cancer is confirmed in different studies. Breast cancer in younger patients appears to be more aggressive (Dubsky et al., 2002; Afsharfard et al., 2013). Some studies in Iran have suggested that the age of Iranian women with breast cancer is at least one decade younger, in comparison with developed countries (Harirchi et al., 2004; Mousavi et al., 2007). According to these studies, the patients in our study were divided into two groups: younger than 40 years and older than 40 years. Studies have revealed that there is an inverse correlation between age and the involvement of axillary nodes (Aitken and Osman, 2010). In this study, patients' age was an independent predictor of NSLNM (OR=0.13; 95% CI, 0.02-0.8). The effect of age on NSLNM has been evaluated in many other studies. However, we found only one study in which age was a predictor of NSLNM (Farshid et al., 2004), and in the other studies, no relationship was found between age and NSLNM.

Multivariate analysis indicated a significant association between PSLNs/TSLNs ratio and NSLNM. This ratio was the strongest predictor of NSLNM in this study. Patients with PSLNs/TSLNs ratio of 100% had a higher likelihood of NSLNM. This finding indicates that patients with at least one negative SLN have a lower risk of NSLNM compared to those with involvement of all SLNs. Similar findings have been reported by Goyal et al. (Goyal et al., 2004). They mentioned that a greater number of negative SLNs indicated a lower lymphatic tumor burden and decreased likelihood of NSLNM.

LVI and ECI were the other two significant predictors of NSLNM in this study with ORs of 19.4 and 13.3 respectively. LVI as a predictor of NSLNM has been reported in several studies (Silverstein et al., 2001; Viale et al., 2005; Bolster et al., 2007; Jinno et al., 2008; Fougou et al., 2009; Alvarenga et al., 2013). LVI, overall metastasis size and PSLNs/TSLNs ratio, were three predicting factors of NSLNM which were reported by Gur et al. (Gur et al.,

2010). In their study, the highest OR belonged to LVI. ECI of the axillary lymph node is an index for aggressive tumor behavior in breast cancer and the patients with ECI have an obvious poorer outcome (Altinyollar et al., 2007). In many studies, ECI was a predictor of NSLNM (Stitzenberg et al., 2003; Van Zee et al., 2003; Ozmen et al., 2006; Beriwal et al., 2008; Fujii et al., 2010; Boler et al., 2012; Derici et al., 2012; Scomersi et al., 2012), although in some other studies this relationship was not found or evaluated (Yu et al., 2005; Wada et al., 2006; Guray Durak et al., 2011). In a meta-analysis by Degmin et al., the size of the SLN metastasis, ECI, primary tumor size, and LVI, were defined as predicting factors of NSLNM (Degmin et al., 2003).

The relationship between the primary tumor size and NSLNM was investigated in several studies, and primary tumor size was considered to be a strong predictor of NSLN involvement. Patients with tumors larger than 20 mm were more likely to have NSLNM (Chu et al., 1999; Wada et al., 2006; Kapur et al., 2007; Friedman et al., 2013), although, this was not shown in a few studies (Abdessalam et al., 2001; Rahusen et al., 2001; Guray Durak et al., 2011; Eldweny et al., 2012). We found that primary tumor size is a significant predictor of NSLNM and patients with a tumor size larger than 20 mm were at increased risk of tumoral involvement in the remaining axillary lymph nodes.

Axillary lymph node involvement has been shown to be higher in ER/PR positive patients in some investigations (Bevilacqua et al., 2007). Van Calster et al. found that ER and HER-2/neu positive tumors have a higher likelihood of axillary lymph node involvement (Van Calster et al., 2009). We did not find any relationship between ER, PR and P53 status and HER-2/neu expression, with NSLNM. Kwon et al., investigated the association of numerous biological markers and NSLNM. They reported that biomarkers are not useful predictors of NSLNM (Kwon et al., 2011).

In this study, no significant relationship was found between PNI, size of SLN metastasis, multifocality of the primary tumor and the number of positive SLNs with NSLNM.

Some investigations have revealed that multifocality of the primary tumor is a predictor of NSLNM (Ozmen et al., 2006; Fougo et al., 2009). In the present study, the relationship between multifocality of the primary tumor and NSLNM was significant in univariate analysis, but it was not significant in multivariate analysis. The reason for this finding may be the low number of patients with multifocal tumors in our study (27 patients).

The size of the SLN metastasis had no significant relationship with NSLNM after multivariate analysis. Some investigations have demonstrated that the presence of micrometastasis in SLN was associated with lower rates of NSLNM, compared to macrometastasis (Chu et al., 1999; Van Deurzen et al., 2007; Baker et al., 2012; Mittendorf et al., 2012). Fougo et al. reported that the size of the SLN metastasis was not an independent predictor of NSLNM (Fougo et al., 2009). The small number of micrometastasis in our study population might be the reason for the differences between our results and other

studies (only 14 patients had micrometastasis in SLN).

Based on the identified predictors of NSLNM in different studies, several nomograms have been developed to predict the presence of tumor in NSLNs in the axilla (Van Zee et al., 2003; Barranger et al., 2005; Kohrt et al., 2008; Pal et al., 2008; Gur et al., 2010; Koca et al., 2014). The most widely used nomogram is developed by Memorial Sloan-Kettering Cancer Center (MSKCC) (Van Zee et al., 2003). This nomogram includes primary tumor size, grade, number of positive and negative SLNs, SLN detection method, ER status, LVI, and tumor multifocality to predict NSLNM. Although the predictive accuracy of these nomograms have been validated, they are not widely used due to their complexity.

The current study had some limitations. In our institution, SLNs are not routinely evaluated with immunohistochemistry methods and this might be a reason for the low incidence of micrometastasis in our patients. In addition, this was a retrospective study and some data were not available for all patients which could have affected our results.

In conclusion, overall, in our study, predicting factors of NSLNM were age, LVI, ECI, primary tumor size, and PSLNs/TSLNs ratio. These factors should be validated in prospective studies in order to develop and validate a nomogram to predict NSLNM in Iranian patients.

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