

# Frequency and Predictors of Axillary Lymph Node Metastases in Iranian Women with Early Breast Cancer

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## Abstract

**Background:** Axillary lymph node metastasis is the most important predictive factor for recurrence risk and survival in patients with invasive breast carcinoma. The aim of this study was to determine factors associated with metastatic involvement of axillary lymph nodes in Iranian women with early breast cancer. **Methods:** This article reports a retrospective study of 774 patients with T1-T2 breast cancer who underwent resection of the primary tumor and axillary staging by SLNB and/or ALND between 2005 and 2015 at our institution. **Results:** Of the 774 patients included in this study, 35.5% (275 cases) had axillary lymph node involvement at the time of diagnosis. Factors associated with nodal involvement in univariate analyses were tumor size, lymphovascular invasion (LVI), tumor grade, ER/PR status and HER2 expression. All factors identified with univariate analyses were entered into a multivariate logistic regression model and tumor size (OR= 3.01, CI 2.01–4.49, P <0.001), ER/PR positivity (OR = 1.74, CI 1.1.16–2.62, P = 0.007) and presence of LVI (OR = 3.3.8, CI 2.31–4.95, P <0.001) remained as independent predictors of axillary lymph node involvement. **Conclusions:** In conclusion, the results of this study suggests that positive hormonal receptor status, LVI and tumor size are predictive factors for ALNM in Iranian women with early breast cancer.

**Keywords:** Breast cancer- axillary lymph node- lymph node metastasis

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## Introduction

Breast cancer is the most common cancer amongst Iranian women and the second most common cause of cancer death (Mousavi et al., 2008; Abedifar, 2009). Despite using several new prognostic factors, histologic axillary lymph node metastasis (ALNM) remains the most important predictive factor for recurrence risk and survival in patients with invasive breast carcinoma (Steele, 1983; Luini et al., 2005). Due to poor sensitivity and specificity of manual clinical examination, axillary lymph node dissection (ALND) has been the standard of care in patients with invasive breast cancer in order to provide correct staging. However, it is associated with complications such as loss of sensation in the arm, reduction of the arm mobility and lymphedema (Maunsell et al., 1993; Taylor, 2004). In recent years, sentinel lymph node biopsy (SLNB) has emerged as an alternative to ALND and has become the standard treatment for axillary staging in clinically node negative patients (Lyman et al., 2005). Despite being a minimally invasive surgical procedure, SLNB is time-consuming and requires a multidisciplinary team that includes the surgeons, a nuclear medicine specialist, a radiologist and a pathologist which may not be feasible, especially where resources are limited (Kitajima et al., 2005). Moreover, it has 15-20% false negative rate which might

lead to a second surgery and a significant increase in cost (Kelley et al., 2004).

Alternative to axillary surgery, either ALND or SLNB, is the use of predictive factors to estimate the risk of nodal involvement. The identification of such factors would be effective in sparing axillary lymph node surgery and reducing subsequent complications, especially for patients with early breast cancer who have the lowest risk of axillary lymph node involvement. Several factors including tumor size, histological grade, lymphovascular invasion (LVI), estrogen and progesterone receptor (ER and PR) status, and HER-2 expression have been identified in various studies as predictors of ALNM but to the best of our knowledge, no study has evaluated this factors in Iranian breast cancer patients (Chua et al., 2001; Viale et al., 2005; Capdet et al., 2009; Lee et al., 2010; Ashturkar et al., 2011; Orang et al., 2013; Toshikawa et al., 2015; Öz et al., 2016). The aim of the present study was to investigate the incidence of nodal involvement and identify clinicopathological predictors of ALNM in Iranian patients with early invasive breast cancer.

## Materials and Methods

Data were obtained from retrospective review of Cancer Research Center (CRC) database of Shohada-e-Tajrish hospital, a tertiary care teaching hospital. We included

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patients with pathologic T1 and T2 invasive breast carcinoma who underwent resection of the primary tumor and axillary staging by SLNB and/or ALND between 2005 and 2015. All patients treated for a local recurrence or metastatic disease, with a carcinoma in situ or those who had received neoadjuvant therapy were excluded from study. In order to determinate factors that are associated with ALNM, each of the following characteristics were retrieved from the database and included in the analysis: age at diagnosis, tumor grade, tumor size, histologic subtype, ER and PR status, HER-2 expression and lymphovascular invasion. Primary tumor size was classified as T1 ( $\leq 20$ mm), T2 ( $20 < \text{size} \leq 50$ mm) according to TNM standards (AJCC, 7<sup>th</sup> edition) (Edge and Compton, 2010). ER and PR receptor status were determined based on the results of immunohistochemistry tests and classified as positive or negative.

All data were analyzed using the SPSS statistical software package (version 24.0; IBM, Inc., Chicago, IL, USA). The  $\chi^2$  test and Fisher's exact probability tests were used for categorical variables, and t-test for continuous variables. The relationship between patient characteristics and axillary lymph node metastases was examined by univariate and multivariable logistic regression analyses. Factors significantly associated with lymph node metastases (P value  $< 0.10$ ) in the univariate analysis were included in a logistic regression model. For the multivariate analyses, p values  $< 0.05$  were considered statistically

significant. Missing data for the predictor variables were handled by multiple imputation.

## Results

Of the 774 patients included in this study, 35.5% (275 cases) had axillary lymph node involvement at the time of diagnosis. Patient and tumor characteristics and results of univariate studies are presented in Table 1.

Patient's median age was 47 years (Range: 17-85). The median primary tumor size was 30 mm (range 3–50 mm). Most of the patients (78.9%) had T2 tumors and only 163 cases had tumors less than 20 mm. The majority of patients had low grade tumors (67%) and invasive ductal carcinoma was the predominant tumor type (92%). Regarding the hormone receptors and HER2 expression, 76.3% of cases were ER/PR positive, and only 25.7% exhibited HER2 overexpression. As depicted in Table 1, factors associated with nodal involvement in univariate analyses were tumor size, LVI, tumor grade, ER/PR status and HER2 expression.

All factors identified with univariate analyses were entered into a multivariate logistic regression model and tumor size (OR= 3.01, CI 2.01–4.49, P  $< 0.001$ ), ER/PR positivity (OR = 1.74, CI 1.1.16–2.62, P = 0.007) and presence of LVI (OR = 3.3.8, CI 2.31–4.95, P  $< 0.001$ ) remained as independent predictors of axillary lymph node involvement (Table 2).

Table 1. Characteristics of the Total Population

Characteristic		All Patients	Node -	Node +	P Value
Age (SD)		48.45 (11.4)	48.15 (11.52)	48.62 (11.34)	0.9
Tumor Size (%)	T1	163 (21.1)	97 (35.3)	66 (13.2)	$< 0.001$
	T2	611 (78.9)	178 (64.7)	433 (86.8)	
LVI (%)	Negative	375 (55.5)	185 (75.2)	190 (44.2)	0.001
	Positive	301 (44.5)	61 (24.8)	240 (55.8)	
Tumor Grade (%)	1,2	480 (67)	190 (74)	290 (63.2)	0.004
	3	236 (33)	67 (26.1)	169 (36.8)	
ER/PR (%)	Negative	183 (23.7)	76 (27.6)	107 (21.5)	0.063
	Positive	589 (76.3)	199 (72.4)	390 (78.5)	
HER 2 (%)	Negative	451 (74.3)	172 (80.4)	279 (71)	0.012
	Positive	156 (25.7)	42 (19.6)	114 (29)	
Pathology (%)	IDC	701 (92)	244 (90.7)	457 (92.7)	0.61
	ILC	43 (5.6)	18 (6.7)	25 (5.1)	
	Mixed	18 (2.4)	7 (2.6)	11 (2.2)	

ER, estrogen receptor; PR, progesterone receptor; LVI, Lymphovascular invasion; IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma

Table 2. Multiple Binary Logistic Regression Analysis for Predicting Clinicopathologic Factors Associated with Lymph Node Metastasis

Variables	P Value	Odd Ratio	95% CI for OR	
			Lower	Upper
High Grade	0.299	1.249	0.819	1.905
ER/PR Negative	0.007	1.745	1.162	2.621
HER2 overexpression	0.087	1.576	0.931	2.668
Presence of LVI	$< 0.001$	3.385	2.313	4.954
Larger Tumor Size	$< 0.001$	3.008	2.014	4.492

ER, estrogen receptor; PR, progesterone receptor; LVI, Lymphovascular invasion; CI, confidence interval

## Discussion

To the best of our knowledge, this is the first study that evaluates incidence and predictive factors for ALNM in a large population of Iranian patients with early breast cancer. The overall incidence of ALNM in present study was 35.5 % which is in line with previous researches from other populations (Silverstein et al., 1995; Chua et al., 2001; Holm-Rasmussen et al., 2015).

In our study, LVI emerged as the most powerful independent predictor of ALNM; the risk for axillary nodal involvement was 3.5 fold greater in the presence of LVI, which is similar to previous findings on the likelihood of axillary lymph node involvement in breast cancer patients (Gajdos et al., 1999; Chua et al., 2001; Viale et al., 2005; Capdet et al., 2009; Lee et al., 2010). Lymphovascular invasion could likely be regarded as prerequisite for the dissemination via the lymphatic (Schoppmann et al., 2004), and all tumors with nodal involvement can be presumed to have had lymphatic invasion whether detected by the pathologist or not. Indeed several studies have shown that intensive pathologic evaluation of axillary lymph nodes by the combined use of hematoxylin-and-eosin-stained levels and immunohistochemical techniques can uncovers occult metastases in 10% to 24% of node-negative patients (Group, 1990; Clare et al., 1997).

Tumor size has been shown consistently to be predictive of ALNM in various studies (Gajdos et al., 1999; Chua et al., 2001; Martin et al., 2002; Ashturkar et al., 2011; Orang et al., 2013; Oz et al., 2016). In this study, patients with tumors larger than 20 mm were three times more likely to have ALNM. However, the reported incidence of ALNM as a function of tumor size varies, ranging from 21 to 42% for T1 tumors and 31 to 63% for T2 tumors. (Chua et al., 2001; Capdet et al., 2009; Marrazzo et al., 2015) In the present study, the incidence of ALNM in T1 and T2 patients were 21.1 and 78.9 respectively. Inconsistency in the incidence of nodal metastases in literature is related to variability of definitions of tumor size that is used: pathological, radiologic or clinical. We applied pathological definitions (AJCC 7th edition) in this research as the clinical and radiological size may overestimate actual size of tumor (Pain et al., 1992).

The present study showed that there was strong association between ER and PR status of tumor with axillary metastasis. Various studies have assessed the role of hormone receptor status in predicting ALNM with conflicting results. Capdet et al. in their study of 1416 early breast cancer patients found no association between hormonal status and nodal involvement (Capdet et al., 2009). In contrast, Lee et al. reported high incidence of ALNM irrespective of the tumor size in Korean population with T1-2 breast carcinoma (Lee et al., 2010). Finally, in a recent study by Holm-Rasmussen et al. ER/PR negative patients had a reduced risk of ALN involvement at the time of diagnosis compared to other patients, when adjusting for other risk factors (Holm-Rasmussen et al., 2015). This difference could be due to different methods of evaluation of ER/PR.

In our series, lack of PR was associated with a two fold increased risk of positive SLN metastases.

According to our findings, although HER2 expression and tumor grade were correlated with axillary metastases in univariate analysis, they did not retain any significant correlation in multivariate analysis. Therefore these factors should not be considered as an indicator for more aggressive treatments.

The main limitation of our study is that it is a retrospective study. Despite this limitation, we consider our results clinically significant because of the large number of cases. Another limitation is that the proliferation marker Ki67 was not included in this study as this variable was not routinely measured and registered in our database in the study period. In conclusion, this large population-based study demonstrates that hormonal receptor status, LVI and tumor size are predictive factors for ALNM in Iranian breast cancer patients.

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