





# Sentinel Lymph Node Metastasis in Invasive Lobular Carcinoma of the Breast

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## ABSTRACT

**Objective:** Invasive lobular carcinoma (ILC) of the breast makes up 5 to 15 percent of all invasive breast cancers. It has distinctive clinical and histopathological features when compared to invasive ductal carcinoma (IDC). This study intends to describe factors influencing sentinel lymph node (SLN) positivity in patients with “pure” ILC.

**Materials and Methods:** Data of 105 patients, who were treated at a tertiary oncology center, with lobular carcinoma of the breast that were subjected to SLN biopsy was probed retrospectively. Patients were categorized as  $\leq 60$  and  $>60$  years of age, positive or negative for estrogen receptor and progesterone, tumor grade I, II and III,  $Ki67 \leq 15\%$  and  $>30\%$ , lymphovascular invasion presence and the presence of multicentricity and multifocality.

**Results:** Mean age at the time of diagnosis was 52 (38-81). Mean tumor size was 2.7 cm (0.7-13cm). Univariate analyses revealed a significant relationship between tumor size ( $\leq 2$  cm vs  $>2$ cm) and metastasis in the SLN. This relation kept its significance in multivariate analyses. ( $p=0.013$ ).

**Conclusion:** With so many different characteristics from IDC, ILC is mostly a uniform tumor. In this study, tumor size was the only independent clinical parameter that was found related to SLN metastases.

**Keywords:** Invasive lobular carcinoma, sentinel lymph node, metastasis

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## Introduction

Invasive lobular carcinoma (ILC) of the breast makes up 5 to 15 percent of all invasive breast cancers (1). It has distinctive clinical and histopathological features when compared to invasive ductal carcinoma (IDC), which is the most common type of breast cancer by far. Patients having ILC are likely to be older and to have larger primary tumors at presentation than patients with IDC (2, 3). Sentinel lymph node (SLN) biopsy is the standard care for clinically node-negative IDC and ILC, although there are very few reports on factors influencing the status of SLN for each tumor subtype in the literature (4-6). This study intends to describe factors influencing SLN positivity in patients with “pure” ILC.

## Materials and Methods

Data of 105 patients, who were treated at a tertiary oncology center, with “pure” lobular carcinoma of the breast that were subjected to SLN biopsy was probed retrospectively. One hundred and six SLN biopsies were performed (one patient with bilateral invasive lobular carcinoma). Primary surgery was mastectomy or breast conserving surgery according to the standard staging of the tumor. SLN(s) was/were sent for frozen section analysis, sliced at 2 mm intervals, and examined under hematoxylin and eosin stain and with immunohistochemistry (IHC) where needed. For those with metastatic (positive) nodes, full axillary lymph node dissection (ALND), involving levels I and II were carried out during the same surgical session. Patients having tumors with invasive ductal component (mixed type) were excluded. Preoperatively detected axillary lymph node involvement was also a reason for exclusion, where a complete axillary dissection was performed straight away.

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The preoperative systemic staging was done performing a routine physical examination, abdominal ultrasound, whole body bone scintigraphy, and computerized tomography (CT), if necessary. Mammography (MG) and breast ultrasound were the standards for breast imaging; magnetic resonance imaging (MRI) was performed if needed. Tc-labeled radioactive tracer and methylene blue dye were used together to identify SLN(s). The following was noted for each patient: age, tumor size, tumor grade, multicentricity and multifocality of the tumor, estrogen receptor (ER) and progesterone receptor (PR) receptor status, c-erb-B2 positivity, Ki67 expression, presence of lymphovascular invasion (LVI), dissected SLN number, positive SLN number, number of SLN with micrometastasis, number of SLN with extracapsular invasion (ECI), number of patients whom ALND was performed, number of dissected lymph nodes during ALND, number of positive lymph nodes after ALND and non-SLN positivity.

Patients were categorized as ≤60 and >60 years of age, positive or negative for ER and PR, tumor grade I, II and III, Ki67 ≤15% and >30%, having LVI presence and the presence of multicentricity and multifocality.

Institutional Review Board approval of Ankara Oncology Research and Training Hospital was granted (2016/114).

This study was performed in compliance with the Declaration of Helsinki.

For this type of study, formal patient consent is not required.

This article does not contain any studies, undertaken by any of the authors, involving human participants or animals.

**Statistical Analyses**

Data was presented as mean, percentage and range and comparison of the data between groups was made with Chi-square and Fisher’s exact tests. For predictive factors affecting SLN positivity, multivariate analysis/Cox proportional hazard regression model was used. A statistical software package for Windows was used for analysis. A p value of ≤0.05 was sought for significance.

**Results**

Mean age at the time of diagnosis was 52 (38-81). Mean tumor size was 2.7 cm (0.7-13 cm). When compared with preoperatively performed imaging studies, actual tumor size in the pathological specimen was greater in 70 patients (66%). According to TNM classification, 36 patients had T<sub>1</sub> (34%) tumors. Most patients had grade II tumors (n=74, 69.8%). ER and PR positivity were present in 98.1% and 87.7% of the patients respectively, whereas c-erb-B2 was positive in only 2.8%. Sixty-nine patients had Ki67 expression lower than 15% compared to 17 who had greater than 30%. LVI was seen in 4.7% of patients. A mean of 2 SLNs was dissected (1-8) in which SLN positivity was found in 29.2% of cases. Primary surgery was a mastectomy in 73 patients, 6 with concurrent reconstruction with a silicone implant. The incidence of non-SLN positivity was 12.3%. Characteristics of the patients and their tumors are given in Table 1.

**Table 1. Patient and tumor characteristics**

Parameter	n (%)
Age in years	
Mean (range)	52±11.3 (38-81)
Tumor size in cm	
Mean (range)	2.7±1.9 (0.7-13)
T classification	
<2cm (T1)	36 (34)
2-5cm (T2)	53 (50)
>5cm (T3)	17 (15)
Bloom-Richardson grade	
I	13 (12.3)
II	74 (69.8)
III	19 (17.9)
Receptor status	
ER (+)	104 (98.1)
PR (+)	93 (87.7)
c-erb-B2 (+++)	3 (2.8)
Ki67<15	69 (65.1)
Multicentricity/multifocality (+)	27 (25.5)
Lymphovascular invasion	5 (4.7)
Sentinel lymph node dissected	
Mean (interval)	2.4±1.4 (1-8)
Patients with metastatic sentinel lymph node	31 (29.2)
Extracapsular invasion (+)	6 (5.7)
Micrometastatic sentinel lymph node	3 (2.8)
Number of metastatic sentinel lymph node	1.4±0.9 (1-5)
Patients who underwent axillary dissection	30
Patients having non-sentinel metastasis	13 (12.3)
Axillary Dissection	
Mean dissected lymph node	17.3±6.3 (7-31)
Mean metastatic lymph node	2 (1-16)
Surgical procedure	
Mastectomy	73 (68.9)
Breast-conserving surgery	33 (31.1)

ER: estrogen receptor; PR: progesterone receptor

**Table 2. Multivariate test result for tumor size**

Tumor size	Patients=n	Patients with positive sentinel lymph node=n (%)	p value	Odds ratio (95% confidence interval)
≤2cm	36	5 (13.8)		
>2cm	70	26 (37.1)	0.013	3.66 (1.26-10.59)

Univariate analysis revealed no significant difference in SLN status when the age of the patient, tumor grade, hormonal receptor status, Ki67 expression, multifocality and multicentricity of the primary tumor and LVI were compared. The only parameter found to be related to SLN positivity was the tumor size. As a multivariate test, logistic regression analysis demonstrated the persistence of significance of the tumor size (Table 2).

## Discussion and Conclusion

Invasive lobular carcinoma is a completely different entity with its unique clinical and pathological features. It arises from the same organ as IDC, and its treatment and outcomes are almost the same as the stage-matched IDC. However, all things in between seem to differ. Clinically, ILC presents more commonly in advanced ages and the breast mass is greater in size at the time of diagnosis (2, 3, 7). In this study mean age of patients with ILC was 52, and mean pathological tumor size was 2.7 cm (T2 tumor). Immunohistochemically, ILC tend to have a high incidence of ER and/or PR expression, making it a more “female” cancer. The c-erb-b2 expression is quite uncommon, and proliferation index, illustrated by Ki67 stain, is lower. These cells are also reluctant to make lymphovascular invasion (8-12). Patients in this study represented a high ER and PR expression, 98.1% and 87.7% respectively. Only 2 (1.8%) were hormone receptor negative. Three tumors (2.8%) were overexpressing c-erb-B2 and only one patient had a triple-negative tumor. Most of the patients (65%) represented a very low proliferation index. LVI in the primary tumor was detected in only five (4.7%).

Pathologically, tumor cells with lobular origin are small and mostly round shaped (9). The most important feature of these cells is the lack of E-cadherin expression, a protein responsible for intercellular adhesion. Therefore, cells are noncohesive and display a single layer arrangement in the tissue (8, 9, 11). This feature may be the reason that preoperative imaging studies underestimated the primary tumor size in 70 cases (66%) in this study. Scattered cells through the breast tissue could explain the high rates of multicentricity/multifocality accompanying ILC (13, 14). One in every four patients had a multicentric/multifocal tumor in this study, presumably contributing to the size mismeasurement encountered with preoperative imaging. A different clinical impact of the loss of cohesion in between ILC cells was underlined by Topps et al. in their study, which interpreted the sensitivity of ultrasound-guided fine needle aspiration biopsy for axillary nodes of ILC patients. The scattered metastasis in the lymph node caused an inferior sensitivity rate for ILC (53.6% vs 98.4% for IDC) (7).

Although conflicting results exist on axillary metastasis of ILC, most studies conclude that they appear to be more in number and greater in size than IDC (7, 12). Almost 30% of clinically node negative cases in this analysis had positive SLN and 43.3% (n=13) of those had additional lymph node involvement in the non-SLNs. One of the few studies comparing axillary node involvement and the ratio of metastatic/dissected axillary nodes between ILC and IDC reported a mean of 4.2 vs 2.12 lymph node metastasis for the grade-matched ILC and IDC respectively (12). With similar grade distribution (grade II>grade III>grade I), our report revealed a mean metastatic axillary node of 2.5. The ratio of metastatic/dissected axillary nodes was 0.13 in this study in contrast to 0.37 in the report above.

Age, tumor size, tumor grade, hormone receptor status, Ki67 value, the presence of multicentricity/multifocality and LVI were tested for

possible predictors of SLN positivity. Univariate analyses revealed a significant relationship between tumor size ( $\leq 2\text{cm}$  vs  $>2\text{cm}$ ) and metastasis in the SLN. This correlation kept its significance in multivariate analyses with an Odds ratio of 3.66 ( $p=0.013$ ) (Table 2). The other factors failed to correlate with SLN involvement. The only paper found in English language literature, focusing on predictive factors of sentinel node metastasis in patients with ILC, was by Grube et al. (15). They found tumor size and age of the patient were predictive factors of metastasis to SLN(s). However, their SLN positivity was 50%, mean age of the patients was more than 60, and their study lacks multivariate analysis of their data.

There are few reports that have investigated the predictive factors for SLN positivity among patients with IDC. Tumor size, vascular invasion, age, menopause status, tumor size, pathological type, hormone receptor status, and tumor location in the Upper outer quadrant were found to have a significant impact on SLN metastasis for IDC (4-6).

With so many different characteristics from IDC, ILC is mostly a uniform tumor. Unexceptionally good prognostic features such as hormone receptor positivity, low expression of c-erb-B2, and low proliferative activity do not seem to correlate with axillary lymph node status. In this study, tumor size was the only independent clinical parameter that was found to be correlated to SLN involvement.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Ankara Oncology Research and Training Hospital (2016/114).

**Informed Consent:** Informed consent was not requested for this study.

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