

Scientific Article

A component of lobular carcinoma in clinically lymph node–negative patients predicts for an increased likelihood of upstaging to pathologic stage III breast cancer

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Abstract

Purpose: Physical examination and diagnostic imaging are often less precise in determining the extent of disease in invasive lobular carcinoma (ILC) relative to nonlobular histologies. Anecdotally, surgical axillary evaluation frequently reveals positive lymph nodes in clinically N0 patients with ILC; however, few studies quantify the likelihood of finding unsuspected disease at the time of surgery. In this study, we evaluate whether the presence of lobular histology increases the incidence of surgical upstaging to pathologic stage IIIA or greater in patients with a clinically node-negative axilla and positive sentinel lymph node (SLN) biopsy.

Methods and materials: We examined patients from our institution between 1997 and 2009 treated specifically with mastectomy, SLN biopsy, and completion axillary lymph node dissection due to a positive SLN. For analysis, patients were grouped according to the presence of any lobular component on surgical pathology. The number of total positive lymph nodes, cancer stage, age, final tumor size, and ER/PR/HER2 status were assessed based on tumor histology.

Results: We evaluated 345 previously untreated women with clinical T0-T2 and N0 disease at the time of surgery. A total of 110 patients (32%) had a component of ILC on surgical pathology. In addition, 295 patients (85.5%) had ER + breast carcinoma, 243 (70.4%) had PR + disease, 56 (16.2%) were HER2 +, and 28 (8.1%) were triple negative. At the time of surgery, women with lobular disease were observed to have a greater number of positive lymph nodes (2.79 vs 2.26; $P = .009$)

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and were more frequently upstaged to at least pathologic stage IIIA compared with nonlobular patients (30.9% vs 17.4%; $P = .007$).

Conclusions: In this cohort, patients with a component of lobular carcinoma were more often surgically upstaged to pathologic stage IIIA or higher, which is a classical indication for postmastectomy radiation therapy. Our findings suggest that ILC is often more extensive than it appears clinically and has significant implications for management of patients with lobular carcinoma after the discovery of a positive SLN.

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Introduction

Except for cancers of the skin, breast cancer is the most frequently diagnosed cancer among U.S. women and accounts for 29% of all new cancer cases and 14% of all cancer-related deaths. In 2017 alone, more than 250,000 newly diagnosed cases of invasive breast cancer and 40,000 deaths were expected.¹ Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) comprise the majority of invasive breast cancer subtypes, with IDC being by far the most common.² However, ILC is often described as the most common special breast cancer subtype because these cancers demonstrate distinct histopathologic features and clinical behavior that distinguish them from other special types and no special type (ductal) carcinomas.

ILC is often associated with several good prognostic factors, including low histologic grade, low proliferative activity, positive expression for hormone receptors, and lack of biomarkers of poor prognosis, such as HER2.³⁻⁶ Despite these lower risk features, the low density of tumor cells in the tissue and absence of a substantial desmoplastic stromal reaction make detection of ILC on physical examination, imaging, and even gross pathologic evaluation more difficult than detection of other histologies.⁷

The same biologic characteristics that lead to later detection of ILC can make it harder for the clinician to find evidence of axillary lymph node (LN) metastases on imaging and physical examination. Nodes may remain nonpalpable, even in extensive metastatic disease. Although several factors aid to predict the presence of LN metastases, including palpable tumor, T-stage, mean tumor size, and angiolymphatic invasion, they are not conclusive.⁸ Only surgical pathology can definitively determine the extent of disease in patients with ILC, and the discovery of LN metastases in a patient originally deemed clinically node-negative can upstage the cancer and significantly alter the treatment plan.

Methods and materials

Patients treated between 1997 and 2009 with mastectomy, sentinel LN biopsy, and completion axillary LN dissection were reviewed. Our institutional review board

examined and approved the study protocol. All participating patients signed an informed consent form for treatment and the use of clinical data in research studies. We retrospectively reviewed the medical records of these patients. Variables including patient demographic information, administered treatment, and clinical outcomes were analyzed. Staging was initially performed with physical examination and imaging.

As per routine clinical practice at our institution, all patients underwent a diagnostic mammogram and ultrasound of the breast and draining LNs during diagnostic and staging workup. Any abnormal nodes seen on ultrasound were subjected to needle biopsy. Patients were classified as having clinical N0 disease if no abnormal-appearing nodes or evidence of metastasis on needle biopsy was found in abnormal appearing nodes. All patients then underwent mastectomy, had a positive sentinel LN biopsy, and underwent a completion axillary LN dissection. Mastectomy was performed per patient preference or at physician discretion in patients unable to undergo breast-conserving surgery.

Patients were grouped according to the presence of any lobular component (ILC and/or lobular carcinoma in situ) on surgical pathology for analysis. Our primary analysis is binary and patients with any lobular features/pure ILC/pure lobular carcinoma in situ were included in the lobular group. All others were included in the nonlobular group. In our secondary analysis, we further divided the lobular group into pure lobular and mixed lobular/ductal. Thus, a patient with IDC having the presence of lobular features would be analyzed in the lobular group for primary analysis and the mixed lobular/ductal group for the secondary analysis.

We evaluated 345 previously untreated women with clinical T0-T2 and N0 disease at the time of mastectomy and sentinel LN biopsy. These patients were found to have a positive sentinel LN and underwent completion axillary LN dissection. We excluded patients with greater than clinical T3-T4 disease, those with biopsy-proven nodal disease, those who had undergone any neoadjuvant chemotherapy or hormone treatment, and those for whom any clinical or pathologic staging information was missing. A review assessed the final surgical pathology reports, number of total positive LNs, cancer stage, age at the time of surgery, presence of lymphovascular stromal invasion (LVSI), final tumor

size, ER/PR/HER2 status, and change to at least American Joint Committee on Cancer (AJCC) version 7 pathologic stage IIIA (T3 N1, any T4, N2, or N3). Fisher's exact test (2-tailed) and the Wilcoxon rank sum test were used to determine significance between groups on univariate analysis. Multivariate analysis was performed on all variables with a significance level of $P < .25$ on univariate analysis. $P < .05$ was considered a significant result in our final analysis.

Results

A total of 110 patients (32%) had a component of ILC on final surgical pathology; 34 of these patients (9.9%) had only lobular components, either pure ILC or ILC/lobular carcinoma in situ, and the other 76 (22%) had an associated mixed/ductal component. A total of 235 patients (68%) had only ductal components. The mean age for all patients was 54 years (range, 28-88 years). Patients with a lobular histology were older (56 vs 53 years; $P = .027$). The mean tumor size was significantly larger in the lobular group (3.1 cm. vs 2.3 cm; $P < .0001$). Lobular patients also had a higher pathologic stage: 35 lobular patients (31.8%) versus 39 nonlobular patients (16.6%) had pathologic stage IIIA or higher, as opposed to stage I and II ($P = .001$). Table 1 provides a descriptive analysis of the 345 patients included in the study.

Women with lobular disease were also observed to have a greater number of positive LNs at the time of surgery (2.79 vs 2.26; $P = .009$), to have less LVSI (39 [35.5%] vs 112 [47.7%]; $P = .034$), to be more likely to have ER + tumors (101 [91.8%] vs 194 [82.5%]; $P = .023$), and to be more frequently upstaged to at least pathologic stage IIIA ($\geq N2$ and/or $\geq T3$) status at the time of surgery compared with nonlobular patients (34 [30.9%] vs 41 [17.4%]; $P = .007$).

Of the entire cohort, 44 patients (12.8%) had additional LNs that were positive after axillary lymph node dissection (ALND); of these, 21 were from the lobular group (21 of 110; 19% incidence) and 23 were from the ductal group (23 of 345; 9.8% incidence). Breaking down the patient group into pure lobular, mixed lobular/ductal, and pure ductal histologies, we found that 41.2%, 28.2%, and 16.4%, respectively, were upstaged ($P = .002$). Of the 34 of 110 (30.9%) pure lobular and mixed lobular/ductal patients who were upstaged, 27 (79%) went on to receive postmastectomy radiation therapy (PMRT) in accordance with historical recommendations. Of the 34 patients with pure ILC, 17 (50%) underwent PMRT, versus 72 of all other patients in the cohort (30.6%; $P = .032$).

On univariate analysis, the presence of LVSI on surgical pathology (odds ratio [OR]: 1.73; 95% confidence interval [CI], 1.23-2.45; $P = .002$), lobular histology (OR: 1.98; 95% CI, 1.38-2.82; $P = .002$), clinical stage T2 (OR: 2.17; 95% CI, 1.07-4.39; $P = .001$), pathologic stage

Table 1 Patient and disease characteristics for lobular (n = 110) and nonlobular (n = 235) patients

Factor	Lobular (n = 110)	Nonlobular (n = 235)	P-value
Age, y	56	53	.027 ^a
Clinical T-stage, n (%)			
T0	14 (12.7)	28 (11.9)	.086
T1	45 (40.9)	121 (51.5)	
T2	51 (46.4)	86 (38.6)	
Hormone receptor status, n (%)			
ER+	101 (91.8)	194 (82.5)	.023 ^a
PR+	85 (77.3)	158 (67.2)	.057
HER2+	13 (11.8)	43 (18.4)	.125
Triple negative	5 (4.5)	23 (9.8)	.097
Pathologic T-stage, n (%)			
T0	0 (0)	3 (1.3)	
T1	42 (38.2)	136 (57.9)	
T2	54 (49.1)	81 (34.5)	
T3	14 (12.7)	14 (6)	
T4	0 (0)	1 (0.4)	
Pathologic mean tumor size, cm.	3.1	2.3	< .0001 ^a
Mean number of positive lymph nodes	2.79	2.26	.009 ^a
Extranodal extension, n (%)	30 (27.2)	38 (16.2)	
Pathologic American Joint Commission on Cancer, 7th Edition stage, n (%)			
I and II	75 (68.2)	196 (83.4)	.001 ^a
III and IV	35 (31.8)	39 (16.6)	
Lymphovascular stromal invasion, n (%)	39 (35.5)	112 (47.7)	.034 ^a
Upstaged after surgery to at least pN2 and/or T3, n (%)	34 (30.9)	41 (17.4)	.007 ^a

Univariate analysis by Fisher's exact test (2-tailed) and the Wilcoxon rank sum test.

^a Statistically significant finding ($P < .05$).

Table 2 Univariate analysis for the odds of having positive lymph nodes on completion axillary lymph node dissection by patient demographic and disease characteristics

	Hazard ratio	95% Confidence interval	Reference	P-value
Lobular histology	1.98	1.38-2.82	Non-lobular	.002 ^a
ER+	1.13	0.68-1.88	Negative	.64
PR+	0.9	0.63-1.31	Negative	.593
HER2 +	1.36	0.84-2.20	Negative	.21
Triple negative	0.57	0.29-1.13	No	.109
Lymphovascular stromal invasion	1.73	1.23-2.45	No	.002 ^a
Multifocal disease	0.97	0.68-1.38	No	.853
Age	1	0.98-1.01	Continuous	.721
Clinical T1	1.52	0.75-3.07	Clinical T0	.001 ^a
Clinical T2	2.17	1.07-4.39		
Pathologic T2	1.78	1.22-2.60	Pathologic T1	< .001 ^a
Pathologic T3 or T4	3.89	2.35-6.43		
AJCC 7 th Edition stage 2	3.81	1.07-13.57	Stage 1	< .001 ^a
AJCC 7 th Edition stage 3	68.35	18.20-256.70		

AJCC, American Joint Commission on Cancer.

^a Statistically significant finding ($P < .05$).

T2 (OR: 1.78; 95% CI, 1.78-2.60; $P < .001$), pathologic stage T3 or T4 (OR: 3.89; 95% CI, 2.35-6.43; $P < .001$), AJCC 7th Edition stage 2 (OR: 3.81; 95% CI, 1.07-13.57; $P < .001$), and AJCC 7th Edition stage 3 (OR: 68.35; 95% CI, 18.20-256.70; $P < .001$) all correlated with an increased number of LNs that were positive at the time of final surgical pathologic evaluation (Table 2).

On univariate analysis, the presence of lobular histology (OR: 2.48; 95% CI, 1.61-3.82; $P < .001$), LVSI (OR: 1.81; 95% CI, 1.19-2.77; $P = .006$), and clinical T2 disease (OR: 1.96; 95% CI, 1.20-3.19; $P < .001$) were significantly associated with upstaging at the time of surgery to at least pathologic stage N2 and/or T3 status. On multivariate analysis, the presence of lobular histology remained significant (OR: 2.34; 95% CI, 1.46-3.73; $P = .004$), as did LVSI (OR: 1.95; 95% CI, 1.22-3.11; $P = .005$) and the presence of clinical T2 disease (OR: 1.67; 95% CI, 1.01-2.76; $P < .001$; Table 3).

To evaluate whether our results apply to all patients with ILC, we also analyzed a cohort of 83 clinically T0-T2 and N0 patients from the same time period who underwent mastectomy and had a negative SLN biopsy but also proceeded with ALND. In this cohort, 5 of 83 patients had a positive LN found at the time of ALND, despite a negative SLN biopsy, for a false-negative rate of 6%. Four of these 5 patients (80%) had a lobular component on final pathology. Only 3 of 83 patients (3.6%) in this negative SLN biopsy cohort were upstaged after surgery to T3 status, and no patients were found to have pathologic N2 stage.

Discussion

ILC often escapes detection by imaging and physical examination due to its covert nature. Several papers discuss the difficulty of detecting ILC on imaging and physical

Table 3 Univariate and multivariate analysis for odds of upstaging to at least pathologic stage IIIA or greater by patient demographic and disease characteristics

Variable	Univariate			Multivariate			Reference group
	Hazard ratio	95% Confidence interval	P-value	Hazard ratio	95% Confidence interval	P-value	
Lobular histology	2.48	1.61-3.82	< .001 ^a	2.34	1.46-3.73	.004 ^a	Non-lobular
ER+	0.86	0.47-1.57	.611				Negative
PR+	0.92	0.58-1.45	.71				Negative
HER2 + disease	1.59	0.91-2.80	.105				Negative
Triple-negative disease	0.46	0.17-1.21	.117				No
Lymphovascular stromal invasion	1.73	1.23-2.45	.006 ^a	1.95	1.22-3.11	.005 ^a	No
Multifocal disease	1.03	0.67-1.60	.8819				No
Age	1.01	0.99-1.02	.528				Continuous
Clinical T2	1.96	1.20-3.19	< .001 ^a	1.67	1.01-2.76	< .001 ^a	Clinical T0 or T1

^a Statistically significant finding ($P < .05$).

examination,^{7,9} but none to date have specifically analyzed the frequency with which surgical upstaging occurs in ILC patients who were initially clinically staged as node-negative. One study by Johnson et al found that the presence of lobular carcinoma predicted for an increased likelihood of having a false-negative axillary ultrasound. Of 155 patients with a negative axillary ultrasound, 6 of 45 with false-negative results had ILC (13%). This is significantly higher than the proportion of patients with ILC in the true-negative group (6 of 110, or 5%; $P < .001$).⁹ Thus, axillary LN metastases may be harder to detect in patients with ILC prior to surgery, resulting in an increased number of positive nodes on surgical pathology.

Previous studies have reported mixed and sometimes contradictory results with regard to the axillary LN status of patients with ILC compared with IDC. Classe et al examined the accuracy of axillary sentinel LN detection among patients with ILC and IDC and found that the axillary sentinel LN detection rate did not differ significantly between patient groups.¹⁰ Similarly, Arpino et al compared the clinical and biological features of 4140 patients with ILC to 45,169 patients with IDC and discovered that although tumor size was significantly larger at the time of diagnosis for ILCs, the rate of LN involvement was the same for both cohorts.¹¹ However, when evaluating the significance of these 2 studies, it is important to recognize that the homogeneous and unremarkable appearance of lobular carcinoma cells (often without cellular atypia or a high mitotic rate) can make this histology more difficult to detect in metastatic LNs. Thus, false-negative results upon examination of surgical specimens are more common in patients with lobular compared with ductal histology.¹²

Contrary to these reports, a French paper analyzed metastatic involvement of ILCs and IDCs in sites other than the axillary nodes and found that the presence of positive nodes in nonaxillary regions was less frequent in patients with ILC than in those with IDC.¹³ Conversely, Fernández et al examined the axillary LN status of patients with grade-matched ILC and IDC and reported a higher nodal stage at the time of surgery, a greater number of total positive nodes, and a higher ratio of positive nodes in patients with ILC.¹⁴ These latter findings correlate with our results—namely, that compared to clinically node-negative patients with IDC, stage-matched patients with ILC were more likely to have a greater total number of positive axillary nodes at the time of surgery and a larger tumor size, upstaging them to require a recommendation of PMRT.

In addition, molecular differences in ILC and IDC may contribute to the increased number of LNs at the time of surgery that we observed in this patient cohort. For example, loss of the cell–cell adhesion molecule E-cadherin is a distinctive molecular characteristic of ILC that allows for tumor cell disruption and invasion. Perhaps due to the loss of proper cell–cell contacts, ILC tends to spread diffusely. Small, uniform populations of neoplastic cells invade the stroma in a single-file fashion without perturbation of anatomic

structures or a significant desmoplastic response.¹⁵ ILC presents in accordance with these histopathologic features, often as an ill-defined palpable mass, vague thickening, or induration as opposed to a discrete nodule.¹⁵ Thus, patients with ILC often present later than those with other subtypes of breast cancer.

In fact, in one large study of 135,157 invasive breast cancer cases from the Surveillance, Epidemiology, and End Results database of the National Cancer Institute from 1992 to 2001, Li et al found that ILC and ductal/lobular carcinoma cases were more likely to have an advanced stage (stage III/IV), large tumor size (>5 cm), and node positivity at the time of diagnosis compared with IDC cases.¹⁶ Thus, ILC's "initially indolent but slowly progressive" nature may allow a longer period of growth before detection,³ which can manifest itself in the increased metastatic potential of ILC.¹³ Regardless, and perhaps due to its favorable biologic characteristics,^{3,6} ILC is associated with better survival outcomes than IDC.^{17,18}

We observed that significantly more clinically node-negative patients with ILC and a positive SLN biopsy were upstaged at the time of surgery to at least pathologic stage IIIA or greater. In patients found to have pathologic stage IIIA or greater disease (AJCC version 7: T3N1, N2-N3, or T4) a recommendation of PMRT is often made, which is consistent with a high level of evidence (category 1) and uniform National Comprehensive Cancer Network consensus that intervention is appropriate.¹⁹

We report that in this cohort of clinically node-negative patients undergoing mastectomy and found to have a positive SLN, >30% of patients with lobular histology were subsequently upstaged at the time of surgery to stage IIIA or greater. Of these patients, 79% actually went on to receive adjuvant PMRT. Thus, we report that even in a small cohort of 34 patients with pure ILC, lobular histology correlated more robustly with an increased likelihood for a surgically upstaged diagnosis, further strengthening our results.

Additionally, given the equivalent results between the arms in the recently published After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) trial that examined ALND versus axillary radiation therapy, our findings may influence the surgical management of the axilla in patients with ILC.²⁰ Our inclusion criteria of clinical T0-T2 patients and a clinically node-negative axilla by ultrasound are very similar to those of the AMAROS trial, which included cT1-T2 patients with no palpable LNs. In the ALND arm of AMAROS, 33% were found to have additional LNs at surgery. Among these, 8% were found to have >4 LNs positive versus 7.5% in the current study. However, no further information was given about the breakdown of lobular versus nonlobular histologies. Thus, given the higher number of positive LNs at ALND, our data may help guide a surgeon's decision on whether to perform completion ALND in clinically node-negative patients on the basis of histology when SLN positivity is found during mastectomy. Likewise, it may help guide the radiation oncologist

in determining the risk of an individual patient with undissected, residual disease in the axilla.

Although the results of our study show a significant difference in occult LN positivity between ILC and non-ILC histologies, it is not without limitations. This is a single-institution, retrospective study that provides a lower level of evidence but suits the current analysis well. Also, despite being stage-matched (clinical T0-2, N0), there are some significant differences between the patient population with regard to age, presence of LVSI, tumor size, and hormone status. This is likely responsible for the lack of significance seen on multivariable analysis. Stratification in a randomized trial could help mitigate these differences and provide stronger evidence on which to base PMRT recommendations, but it is also unlikely that a trial evaluating this question will ever be performed.

It is also important to note that our results only apply to patients who were found intraoperatively to have a positive SLN. The reason for mastectomy in these patients with early stage or even noninvasive breast cancer is unknown. We observed that in a cohort of clinically stage-matched patients who underwent mastectomy and had a negative SLN biopsy, 5 of 83 (6%) had a false-negative result, which is in agreement with the false-negative rates in the literature.²¹ Interestingly, 4 of these 5 patients (80%) had a component of lobular on histology.

Conclusions

Clinically node-negative patients with a component of lobular carcinoma and/or LVSI undergoing total mastectomy and found to have a positive SLN are more likely to be surgically upstaged to at least pathologic stage IIIA than patients with nonlobular histologies. Also, patients with a lobular breast cancer component have a higher risk of residual axillary disease if completion ALND is not performed after an intraoperative finding of a positive SLN. Our findings suggest that the presence of a component of lobular carcinoma may predict for more extensive disease than is clinically apparent and may have significant implications for how clinicians counsel patients with breast cancer with similar features.

References

- American Cancer Society. Cancer Facts & Figures; 2017. Available at <https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html>. Accessed September 2017.
- Dossus L, Benusiglio PR. Lobular breast cancer: Incidence and genetic and non-genetic risk factors. *Breast Cancer Res*. 2015;17:546.
- Rakha EA, El-Sayed ME, Powe DG, et al. Invasive lobular carcinoma of the breast: Response to hormonal therapy and outcomes. *Eur J Cancer*. 2008;44:73-83.
- Domagala W, Markiewski M, Kubiak R, Bartkowiak J, Osborn M. Immunohistochemical profile of invasive lobular carcinoma of the breast: Predominantly vimentin and p53 protein negative, cathepsin D and oestrogen receptor positive. *Virchows Arch A Pathol Anat Histopathol*. 1993;423:497-502.
- Sastre-Garau X, Jouve M, Asselain B, et al. Infiltrating lobular carcinoma of the breast: Clinicopathologic analysis of 975 cases with reference to data on conservative therapy and metastatic patterns. *Cancer*. 1996;77:113-120.
- Rakha EA, El-Sayed ME, Menon S, Green AR, Lee AHS, Ellis IO. Histologic grading is an independent prognostic factor in invasive lobular carcinoma of the breast. *Breast Cancer Res Treat*. 2008;111:121-127.
- Johnson K, Sarma D, Hwang ES. Lobular breast cancer series: Imaging. *Breast Cancer Res*. 2015;17:94.
- Grube BJ, Hansen NM, Ye X, Giuliano AE. Tumor characteristics predictive of sentinel node metastases in 105 consecutive patients with invasive lobular carcinoma. *Am J Surg*. 2002;184:372-376.
- Johnson S, Brown S, Porter G, et al. Staging primary breast cancer. Are there tumour pathological features that correlate with a false-negative axillary ultrasound? *Clin Radiol*. 2011;66:497-499.
- Classe JM, Loussouarn D, Campion L, et al. Validation of axillary sentinel lymph node detection in the staging of early lobular invasive breast carcinoma: A prospective study. *Cancer*. 2004;100:935-941.
- Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: Tumor characteristics and clinical outcome. *Breast Cancer Res*. 2004;6:R149-R156.
- MacGrogan G, Jollet I, Huet S, et al. Comparison of quantitative and semiquantitative methods of assessing MIB-1 with the S-phase fraction in breast carcinoma. *Mod Pathol*. 1997;10:769-776.
- Ferlicot S, Vincent-Salomon A, Médioni J, et al. Wide metastatic spreading in infiltrating lobular carcinoma of the breast. *Eur J Cancer*. 2004;40:336-341.
- Fernández B, Paish EC, Green AR, et al. Lymph-node metastases in invasive lobular carcinoma are different from those in ductal carcinoma of the breast. *J Clin Pathol*. 2011;64:995-1000.
- Rakha EA, Ellis IO. Lobular breast carcinoma and its variants. *Semin Diagn Pathol*. 2010;27:49-61.
- Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. *Br J Cancer*. 2005;93:1046-1052.
- Wasif N, Maggard MA, Ko CY, Giuliano AE. Invasive lobular vs. ductal breast cancer: A stage-matched comparison of outcomes. *Ann Surg Oncol*. 2010;17:1862-1869.
- Hsiao YH, Tsai HD, Chou MC, Man YG. The myoepithelial cell layer may serve as a potential trigger factor for different outcomes of stage-matched invasive lobular and ductal breast cancers. *Int J Biol Sci*. 2011;7:147-153.
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Breast cancer. Version 3.2017. 2017:1-204.
- Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15:1303-1310.
- Pesek S, Ashikaga T, Krag LE, Krag D. The false-negative rate of sentinel node biopsy in patients with breast cancer: A meta-analysis. *World J Surg*. 2012;36:2239-2251.