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ScienceDirect

EJSO 40 (2014) 1245–1249

EJSO the Journal of Cancer Surgery

www.ejso.com

Synchronous lobular carcinoma *in situ* and invasive lobular cancer: Marker or precursor for invasive lobular carcinoma

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Accepted 11 April 2014
Available online 25 April 2014

Abstract

Aim: Lobular carcinoma *in situ* (LCIS) is a known risk factor for invasive breast carcinoma, but there is increasing data indicating a possible precursor relationship. This study investigates the incidence of lobular carcinoma *in situ* that occurs with invasive lobular carcinoma (ILC).
Methods: Women diagnosed with ILC or LCIS from 2000 to 2010 were retrospectively identified and reviewed after institutional review board approval. This group was divided into two cohorts: ILC alone, and LCIS and ILC (ILC/LCIS). Patient demographics, disease characteristics, and treatment modalities were captured. $p < 0.05$ is considered significant.
Results: A total of 148 patients with ILC or LCIS were identified. Forty-four (54%) patients with only ILC, and 37 (46%) patients with ILC/LCIS were identified. Median age at diagnosis was 62 for ILC and 64 years for ILC/LCIS ($p = 0.8$). In patients with ILC, total mastectomy was the predominant treatment modality in 28 of 44 (64%) patients, while 18 of 37 (49%) patients with ILC/LCIS underwent breast conservation therapy ($p = 0.3$). Median largest tumor diameter was 35 mm (range 1–110) for ILC, and 15 mm (range 5–85) for ILC/LCIS ($p = 0.03$). Nodal status was positive in 17 of 39 (44%) ILC and 13 of 34 (38%) ILC/LCIS ($p = 0.6$).
Conclusions: The 46% incidence of LCIS associated with ILC in our cohort study is similar to that reported for ductal carcinoma *in situ* identified with invasive ductal carcinoma at ~40%. The association of pre-invasive and invasive lobular lesions should be further studied in a large scale prospective study to assess for a precursor relationship.

Keywords: Lobular carcinoma; Lobular carcinoma *in situ*; Outcome; Precursor; Breast

Introduction

Arising from the terminal ducto-lobular unit of the breast, lobular carcinoma *in situ* (LCIS) is a histologic entity that is distinct from ductal carcinoma *in situ* (DCIS). While the true incidence of LCIS in the general population is difficult to ascertain given the lack of distinct clinical or radiographic findings, it is estimated to be 3.19 per 100,000 women.[1,2] While it is often an incidental finding on surgical specimens, rates of LCIS diagnosis have increased due to rising sampling of mammographic findings and improved pathologic diagnosis.[1,3] Given the lack of association with microcalcification or visible architectural changes, LCIS is difficult to detect on mammography and hence challenging to diagnose.[4,5]

Despite its indolent growth pattern, LCIS portends an 8–10 fold increased risk of subsequent breast cancer.[6,7] A recent large Surveillance, Epidemiology, and End Results (SEER) analysis confirmed various institutional series that LCIS is a risk factor for subsequent invasive lobular or ductal carcinoma in either breast.[8] There is a small but growing body of evidence suggesting that LCIS may also be a precursor to invasive ductal cancer (IDC) and invasive lobular cancer (ILC). In an analysis of LCIS adjacent to ILC, DeLeeuw et al. reported loss of E-cadherin expression, and Vos et al.

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http://dx.doi.org/10.1016/j.ejso.2014.04.007

noted loss of heterozygosity of wild type E-cadherin allele and truncation of the E-cadherin gene.[9,10] More recent evidence supports the clonal relatedness between proximally located LCIS and ILC lesions.[11–14]

It is well accepted that DCIS is present in almost 40% of samples of IDC.[15] Much has been reported about the incidence of ILC and LCIS as separate entities, but less is known about the coexistence of LCIS with ILC. The increased incidence of both LCIS and ILC over the last two decades can have important ramifications for future classification and management of breast cancer patients. The purpose of this paper is to report incidence of LCIS in proximity to ILC at a single academic institution.

Methods

Women diagnosed with ILC or LCIS from 2000 to 2010 at Ellis Fischel Cancer Center at the University of Missouri, were retrospectively identified from a list obtained through the institutional cancer control registry. Patient records were reviewed after institutional review board (IRB) approval for this project was obtained. Diagnostic evaluation involved history and physical, and appropriate imaging to assess for metastatic disease. Patients underwent pretreatment imaging of the affected breast, and all lesions were histologically confirmed either on biopsy, breast conserving resection, or total mastectomy by pathologists at our institution. Sentinel lymph node biopsy, and subsequent axillary lymph node dissection if necessary, were performed in selected patients with concern for the regional disease. Patient demographics, disease characteristics, treatment modalities, and outcomes were captured from electronic medical records. Surgical staging was captured using the American Joint Committee and Cancer 7th edition.[16]

Statistical analysis was performed using SAS software, version 9.3 (SAS Institute, Cary, NC). Patients were divided into two cohorts for analysis: patients with ILC alone, and patients with LCIS in proximity to ILC (ILC/LCIS). Time to recurrence was calculated from date of diagnosis to date of first local, regional, or distant recurrence. Overall survival was calculated from date of surgical resection, or biopsy if no surgery was performed, to date of last follow-up if alive, or date of death. Local recurrence was defined as ipsilateral breast recurrence with breast conservation therapy (BCT), or ipsilateral chest wall in mastectomy. The univariate analysis of patients, tumor characteristics and treatment modalities was performed using chi-square and Wilcoxon rank sum. Multivariate analysis of various clinical and surgical parameters was performed using logistic regression analysis. p values <0.05 were considered significant.

Results

Pure LCIS was identified in 15 patients, ductal, mixed, or not otherwise specified in 26, and 19 patients were excluded due to incomplete records. ILC was identified in 81 patients, of which 37 (46%) had associated LCIS in proximity to invasive lobular carcinoma. Most patients were white (96%). Median age for the entire cohort, ILC, and ILC/LCIS was 63 (range 29–88), 62 (range 29–88), and 64 years (range 30–85), respectively. For the entire cohort, 37 diagnoses were made clinically, and 44 radiographically utilizing mammogram, ultrasound, or magnetic resonance imaging (MRI). Surgical treatment was mastectomy in 45 (46%) patients and BCT in 33 (41%) patients. In patients with ILC, mastectomy was the predominant treatment modality in 28 (64%), while only 17 (46%) patients with ILC/LCIS underwent mastectomy. Essentially all tumors were ER positive (99%). Univariate analysis of stage, method of initial diagnosis, surgical diagnosis, surgical extent, lymph node evaluation, tumor size, nuclear grade, and surgical margins can be found in Table 1. Median largest tumor diameter was 35 mm (range 1–110) for ILC, and 15 mm (range 5–85) for ILC/LCIS patients, and greater than 50 mm in 1 patient ($p = 0.03$).

Table 1
Treatment and surgical pathology characteristics by histology.

	ILC ($n = 44$)	ILC/LCIS ($n = 37$)	p value
AJCC stage			
1	11 (25%)	15 (41%)	0.54
2	19 (43%)	12 (32%)	
3	11 (25%)	8 (22%)	
4	1 (2%)	–	
Other	2 (5%)	2 (5%)	
Method of initial diagnosis			
Clinical exam	23 (52%)	14 (38%)	0.19
Mammogram	17 (39%)	18 (48%)	
Ultrasound	4 (9%)	4 (11%)	
MRI	–	1 (3%)	
Surgical diagnosis			
Excisional	8 (18%)	12 (32%)	0.33
Core	31 (71%)	21 (57%)	
Unknown or other	5 (11%)	4 (11%)	
Surgical extent			
Mastectomy	28 (64%)	17 (46%)	0.26
Less than mastectomy	15 (34%)	18 (49%)	
Biopsy	1 (2%)	2 (5%)	
Lymph node evaluation			
Negative	22 (50%)	21 (57%)	0.80
Positive	17 (39%)	13 (35%)	
Unknown	5 (11%)	3 (8%)	
Tumor size			
Largest diameter (mm) (range) ($n = 74$)	35 (1–110)	15 (5–85)	**0.03**
Nuclear grade			
Grade 1	16 (36%)	14 (38%)	0.11
Grade 2	14 (32%)	19 (51%)	
Grade 3	4 (9%)	1 (3%)	
Unknown	10 (23%)	3 (8%)	
Margins			
Negative	29 (66%)	24 (65%)	0.75
Close (<1 mm)	3 (7%)	5 (13.5%)	
Positive	4 (9%)	3 (8%)	
Unknown	8 (18%)	5 (13.5%)	

AJCC: American Joint Commission on Cancer.