Comparative Long-term Study of a Large Series of Patients with Invasive Ductal Carcinoma and Invasive Lobular Carcinoma. Loco-Regional Recurrence, Metastasis, and Survival

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Abstract: Our aim was to compare histologic and immunohistochemical features, surgical treatment and clinical course, including disease recurrence, distant metastases, and mortality between patients with invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC). We included 7,475 patients operated for 7,899 breast tumors, with 1,639 IDC (1,600 patients) and 145 patients with ILC and 150 breast tumors. The median follow-up was 76 months. ILC was significantly more likely to be associated with a favorable phenotype. Prevalence of contralateral breast cancer was slightly higher for ILC patients than for IDC patients (4.0% versus 3.5%; p = n.s). ILC was more likely multifocal, estrogen receptor positive, Human Epidermal Growth Factor Receptor-2 (HER2) negative, and with lower proliferative index compared to IDC. Considering conservative surgery, ILC patients required more frequently re-excision and/or mastectomy. Prevalence of stage IIB and III stages were significantly more frequent in ILC patients than in IDC patients (37.4% versus 25.3%, p = 0.006). Positive nodes were significantly more frequent in the ILC patients (44.6% versus 37.0%, p = 0.04). After adjustment for tumor size and nodal status, frequencies of recurrence/metastasis, disease-free and specific survival were similar among patients with IDC and patients with ILC. In conclusion, women with ILC do not have worse clinical outcomes than their counterparts with IDC. Management decisions should be based on individual patient and tumor biologic characteristics rather than on lobular versus ductal histology.

Key Words: breast neoplasms, invasive ductal carcinoma, invasive lobular carcinoma, mortality, neoplasm recurrence, survival

BACKGROUND

Invasive lobular carcinoma (ILC) is the second most common histologic type of breast cancer. Prevalence ranges widely from 5% to 20%, owing to well-known
discrepancies concerning its histopathologic definition (1,2). ILC is made of small cells with irregular round to oval nuclei and occasional intracytoplasmic vacuoles. Cells tend to be noncohesive because of loss of the adherence protein E-cadherine. Mitoses are scant. Cell invades the stroma on single lines. ILC cells form concentrical (bull’s eye) cords. All such features conform to the ILC classical pattern.

The Not Otherwise Specified invasive breast carcinoma known as “invasive ductal carcinoma” (IDC) is made of variable-size malignant cells that present invasive trabecular, gland-like or solid patterns, also occasionally with a cord-bull’s eye pattern of individual cells. Cells are quite large and have regular/pleomorphic nuclei with prominent nucleolus, and rich eosinophilic cytoplasm.

Although there are a few differences between lobular and ductal invasive tumors on mammography, predicting breast cancer histology becomes quite difficult based on image presentation alone. Some authors indeed point to substantial differences between IDC and ILC in image-diagnosis presentation, multifocality, tumor size, and patient age at the time of primary surgery (1,3,4). Also, some differences have been noticed in the immunohistochemical profile, with ILC showing an increased rate of positive hormone receptors and a decreased rate of Her2-neu expression, notwithstanding the fact that its single most important feature is the presence of E-cadherine and p120 catenine (5). Others believe ILC is associated with a specific metastatic spread pattern to the gastrointestinal tract and pelvis, whereas IDC spreads to lung, bone and central nervous system (6). It seems that both tumors are considered well separated in the literature, with a veiled intuition of worse prognosis for ILC.

Our aim was to compare histologic and immunohistochemical features, surgical treatment and clinical course, including disease recurrence, distant metastases, and mortality of patients with IDC and ILC.

**PATIENTS AND METHOD**

Consecutive breast cancer patients referred to the Breast Unit of the University Hospital MútuaTerrassa and Hospital of Terrassa for surgical treatment were prospectively included (1997–2013). Patients with in situ carcinomas and those unfit for surgery were excluded.

The Kaplan–Meier and log-rank tests were used to calculate and compare survival rates. A multivariate analysis was used based on the Cox proportional hazard method. Statistical analysis was performed using SPSS 17.0 (SPSS, Chicago, IL).

This study was done in accordance with the Review Board and Ethics Committee. Written informed consent was always obtained before any invasive procedure and surgery.

**RESULTS**

We included 1,745 patients operated for 1,789 breast tumors, 1,600 of whom presented 1,639 (91.6%) IDC, and 145 of whom showed 150 (8.4%) ILC.

Clinical and pathologic features of patients are displayed in Table 1. Compared with IDC, ILC tumors in our series had a higher chance of being multifocal/multicentric and presented positive estrogen and progestosterone receptors, and Her2 negative (luminal A or B), also with lower proliferative index. Patients with ILC have higher tumor burden and, therefore, higher incidence of IIIA or greater.
The surgical treatment is described in Table 2. Regarding patterns of local-recurrence and metastatic spread in ILCs and IDCs, there were no between-group differences in local relapse or metastatic spread, overall or per organ, except for peritoneal spread that was seven times higher in ILC (2.1%) than in IDC (0.3%; p = 0.015). Prevalence of contralateral breast cancer was slightly higher for ILC patients than for IDC patients (4.0% versus 3.2%; p = n.s).

The occurrence of second, nonbreast neoplasia was not significantly different between histologic types: 5.5% for ILC and 4.5% for IDC.

There were no significant differences in overall or specific mortality, nor in survival time between ILC and IDC (Table 3; Fig. 1).

**DISCUSSION**

Clinico-pathologic features and long-term results were compared in a large cohort of patients with either ILC or IDC.

**Clinico-Pathologic Features**

This study shows specific clinico-pathologic traits in our local population of ILC patients, although there were no significant differences with IDC patients in mortality or distant relapse.

Compared with IDC, patients with ILC tend to have larger, multifocal/multicentric tumors that are well differenciated (1,4), with less vascular invasion and less tumoral necrosis. However, they tend to display more lymphatic invasion with corresponding greater rate of axillary lymph-node positivity and stage IIB and IIIA disease. Nevertheless, they show higher rates of luminal A subtype tumors and half the rate of triple-negative tumors (1,7). Such data are inconsistent with the report by Arpino (1).

Mean age at onset was quite similar for both groups. At odds with others, but in agreement with Biglia (1), age was not a differential factor between ductal and lobular carcinomas.

The ability of ILC to escape early diagnosis may well be the reason for differences in tumor size compared with IDC. In our study, over one-third of ILC and IDC patients were diagnosed through a mass-screening program. Contrary to other experiences (5), there were significant differences in tumor size across histologic types.

Increased tumor size could be explained on ILC histologic grounds, as cells invade connective tissue in lines, are not cohesive, and do not elicit a desmoplastic reaction which makes self-detection even more difficult. Such appearance makes it difficult for the radiologist, as oftentimes imaging is misleading. From the advent of magnetic resonance imaging (MRI), disease extent can be better approached although there is still a histologic versus image inconsistency in both histologic types. In some cases, overestimation of tumor size by MRI may lead to mastectomy thereby increasing patient and doctor concern as well as healthcare costs.

Some authors believe lymph-node involvement (8) is the single most important prognostic factor for

### Table 2. Surgical Treatment

| Invasive carcinoma | IDC (N = 1,639) | ILC (N = 150) |
|--------------------|----------------|--------------|
| Initial surgical treatment* | 1,191 (72.7%) | 86 (57.4%) |
| Mastectomy* | 364 (22.2%) | 59 (39.3%) |
| Chemotherapy neoadjuvant* | 84 (5.1%) | 5 (3.3%) |
| Close/positive margins after lumpectomy* | 688 (42%) | 49 (33%) |
| Second surgery* | | |
| Subsequent breast-conserving re-excision* | 584 (49.0%) | 37 (43.0%) |
| Subsequent mastectomy* | 177 (14.8%) | 24 (27.9%) |
| Overall surgical treatment* | 1,098 (67.0%) | 67 (44.7%) |
| Total number of BCS | 541 (33.0%) | 83 (55.3%) |
| SSNB | 867 (53.5%) | 71 (47.3%) |
| Axillary | 862 (99.4%) | 71 (100%) |
| Internal mammary | 67 (7.7%) | 5 (7.0%) |
| SSNB positive | 214 (24.7%) | 22 (31.0%) |
| SSNB negative | 653 (75.3%) | 49 (69.0%) |

* p < 0.05, statistically significant differences among IDC and ILC using the chi-squared test.

BCS, Breast conservation surgery; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; SSNB, selective sentinel node biopsy.

### Table 3. Multivariate Analysis. Hazard Ratios (95% CI) for Overall and Specific Survival, According to Invasive Ductal Carcinoma or Invasive Lobular Carcinoma after Adjusting for Age, Stage, Histologic Grade, Receptors, and Multifocal

| Invasive carcinoma | Metastasis | Disease-free survival | Overall survival | Specific survival |
|--------------------|------------|-----------------------|-----------------|------------------|
| Ductal | 1.000 | 1.000 | 1.000 | 1.000 |
| Lobular | 1.288 (0.822-2.017) | 1.473 (0.991-2.189) | 1.157 (0.763-1.755) | 1.178 (0.680-2.040) |
patient survival in breast cancer, although recent studies have shown that alternative immunohistochemical factors overtake lymph-nodes in breast cancer prognosis (9,10), histology not regarded.

**Surgical Treatment**

Because one third of ILC cases present multifocality and because ILC is often difficult on radiologic studies, some authors seem concerned about the feasibility of breast-conserving treatment. In our experience, radical surgery was significantly more prevalent in ILC than in IDC patients.

Considering breast-conserving surgery, prevalence of margin re-excision was significantly higher in IDC patients, which differs from others (5).

We have been performing sentinel node biopsy (SNB) since 2002. Similar to most authors (11), but contrary to some (4), histology of the primary was not taken as an exclusion criterion for SN. Nevertheless, the rate of effective SNB was 22% lower in ILC patients.

**Mortality**

In spite of immunohistochemical differences between ILC and IDC, we did not find significant differences in overall mortality or in specific mortality. Survival rate was over 90% in both groups, which is quite similar to other studies with equivalent follow-up periods (1,7).

**Loco-Regional and Distant Relapse**

It has been suggested that IDC and ILC display a differential pattern of metastatic spread. In agreement with Cao (3), we have shown an increased overall prevalence of metastases but not in their particular organ distribution. A few studies have addressed the relationship between margins of resection status and local relapse. Some authors have reported a slight increase in local relapse for patients undergoing breast-conserving surgery, although it is unclear (8). Breast-conserving surgery entails tumor excision together with a sufficient disease-free margin of breast tissue. Therefore, it is advisable to perform an intraoperative specimen assessment, which obviously leads to an increase in intraoperative re-excision and eventually to re-operation. Similar to our own experience, recent studies have not shown differences in local relapse (1,3). By contrast, Cao (3) found a significant, almost double increase in contralateral breast relapse in ILC. Considering the pre-MRI era, the question remains whether these were cases of true relapse or underdiagnosed bilateral neoplasias.

**CONCLUSIONS**

Invasive lobular carcinoma patients have increased rates of involved nodes, greater tumor burden, greater tumor size, thereby including more patients with stage IIIA and are more often multifocal; however, they do not show worse mortality rates.
In our cohort, patients with ILC had similar likelihood of death than patients with IDC. This might be due to they tend to fall into more risk-favorable immunohistochemical subtypes, have less lymphovascular invasion, and lower proliferation rates.

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CONFLICTS OF INTEREST

None.

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