EPIDEMIOLOGY

Impact of invasive lobular carcinoma on long-term outcomes in Mexican breast cancer patients

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Abstract

Purpose The aim of this study was to compare the difference in disease-free survival (DFS) and overall survival (OS) between invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC) in our Hispanic population with breast cancer (BC).

Methods We retrospectively analyzed a database of 4533 non-metastatic BC patients treated for BC at the National Cancer Institute in Mexico (INCan) between 2006 and 2016. We compared clinical characteristics, treatment and survival between women with invasive ductal and invasive lobular BC. We evaluated differences between survival curves with the log-rank test and used Cox's proportional hazards model for the multivariate analysis.

Results Median follow-up time was 42.13 months (IQ_{25} 25.2–IQ_{75} 72.06). The median age was 50.9 years (IQ_{25} 43.5–IQ_{75} 59.8). DFS at 5 years was 80.8% for IDC versus 76.2% for ILC. 5 years OS was 88.7% for IDC versus 84.3% for ILC. Multivariate analysis showed that factors that negatively affected the 5-year DFS include: clinical stage III [hazard ratio (HR) 4.2, 95% CI 3.36–5.35; $p < 0.001$], triple negative phenotype (HR 1.4, 95% CI 1.08–1.81; $p = 0.009$), Ki67 ≥ 18 (HR 1.6, 95% CI 1.28–2.11; $p < 0.001$), and lobular histological type (HR 1.6, 95% CI 1.09–2.49; $p = 0.017$). Factors associated with a negative impact on OS were: clinical stage III (HR 4.5, 95% CI 3.15–6.54; $p < 0.001$), triple negative phenotype (HR 2.4, 95% CI 1.69–3.48; $p < 0.001$), and Ki67 ≥ 18% (HR 1.9, 95% CI 1.27–2.92; $p = 0.02$).

Conclusion Our results highlight the different biology of ILC and show that long-term prognosis in terms of DFS is not as favorable as previously reported.

Keywords Lobular carcinoma · Disease-free survival · Breast cancer

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Introduction

It is well known that breast cancer (BC) is a heterogeneous disease [1, 2]. Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) are the two most frequent histologic subtypes [1]. Both have different outcomes according to specific immunohistochemical phenotypes [2, 3]. ILC presents diagnostic challenges as it is associated with the frequent absence of a grossly evident mass upon physical examination and with the absence of distinct mammographic characteristics [4, 5]. ILC is characterized microscopically by linear growth along mammary ducts, forming thin masses with a single-file pattern which infiltrates the adjacent tissue without destruction of anatomic structures and with minimal inflammatory response [6–8]. In addition to this atypical growth pattern, ILC has distinct biologic features, including a high frequency of bilateral presentation (one third of

patients), multifocality and multicentricity (more than 50% of patients) [6, 8, 9], and a specific pattern of metastatic spread which commonly includes the lungs, ovaries, and gastrointestinal tract [8, 9].

Lobular carcinoma represents 5–15% of all BC cases [2, 10–13], and it is typically characterized as having a low percentage of Ki67 expression, high estrogen receptor (ER) and progesterone receptor (PR) expression and less frequent HER2 overexpression when compared with IDC. Because of these pathologic features, ILC has been frequently considered to have a more favorable prognosis [2, 7, 14–16]. However, despite these characteristics, there are conflicting data regarding long-term outcomes, with some stage-matched analyses showing that disease-free survival (DFS) and overall survival (OS) are superior for IDC compared to ILC [1, 8, 17–19], while other reports have found that histology has no effect on survival [1, 6–8, 10, 14, 17, 20]. The aim of this study was to identify if ILC has an impact on DFS and OS when compared to IDC histology in our Hispanic population with BC.

Patient and methods

Patients with clinical stage I–III invasive ductal and invasive lobular BC were selected from a database of 5524 BC patients treated under a government sponsored social security program named "Seguro-Popular" at the National Cancer Institute Mexico (INCan) between 2006 and 2016. We excluded patients with mixed and other pathology types. The pathology report was required to include ER and PR expression and HER2 status, with or without Ki67 evaluation. Complete staging workup and treatment information were mandatory for inclusion. The Institutional Review Board approved this review.

Two breast pathologists reviewed histological type, grade, and phenotype. We collected clinical and pathologic characteristics, treatment modalities and clinical outcomes. Complete pathological response was defined as the absence of invasive tumor in the breast and axillary nodes after neoadjuvant systemic treatment; the presence of in situ component in the breast tissue was allowed (ypT0-ypTis, ypN0) [21]. DFS was calculated from the date of diagnosis to the date of disease relapse. OS was calculated from the date of diagnosis to the date of death from any cause and was censored at the date of the last follow-up interview.

Patient population

Estrogen, progesterone, and HER2 status were evaluated according to the ASCO-CAP guidelines [22, 23]. We classified BC patients into three phenotypes according to the expression of ER, PR, HER2 by immunohistochemistry;

triple negative (ER−/PR-/HER2-), HER2+ (ER/PR− or +/ HER2+) and hormone-sensitive (ER+ or PR+/HER2−). BC staging was performed according to the seventh edition of the American Joint Committee on Cancer [24]. We defined locally-advanced disease as stages to IIB to IIIC.

Neoadjuvant and adjuvant chemotherapy was based on anthracycline–taxane therapy. Patients with HER2 overexpression received trastuzumab as part of their treatment. Physicians chose the oncologic treatment based on national guidelines and on the decisions of the Multidisciplinary Tumor Board meetings carried out at our Breast Cancer Department, INCan [25].

Statistical analysis

A descriptive analysis of the clinical, pathological and treatment variables was done, stratifying by menopausal status, histology type, percentage of Ki67 expression (using 18% as a cutoff point), nuclear grade, body mass index, clinical stage, and presence of diabetes or hypertension. The χ^2 test was used to compare the distribution of characteristics among groups according to IDC versus ILC, and a p value of < 0.05 was considered statistically significant.

We reported 5-year OS and DFS for the stratifying study variables according to histological type. DFS and OS were estimated with the Kaplan–Meier method and were compared between groups using the log-rank test. We used the Cox's proportional hazards model for the multivariate analysis, defining the percentage of hazard ratio (HR) with 95% confidence intervals. The statistical software Stata version 14 and the statistical software R version 3.3.1 were used for the statistical analysis.

Results

A total of 4533 patients met the inclusion criteria for analyses (Fig. 1). Median follow-up time was 42.13 months (IQ$_{25}$ 25.20–IQ$_{75}$ 72.06). The median age was 50.9 years (IQ$_{25}$ 43.5–IQ$_{75}$ 59.8). Patients with ILC were older than patients with ductal invasive carcinoma, with a higher proportion classified as post-menopausal. We did not find a significant difference between ILC and IDC with regards to having a higher body mass index, obesity, or diabetes. The distribution of clinical stage I–II and III was comparable by histologic type. Lobular tumors had a lower proliferative index measured by percentage of Ki67, were mostly low nuclear grade and had a greater proportion of hormone-sensitive tumors, with a lower proportion of HER2+ and triple negative subtypes. Table 1 shows the clinical and pathologic characteristics according to histologic type.

Concerning treatment modality, we did not find differences regarding the type of surgery and administration of

Fig. 1 Breast cancer patients and distribution
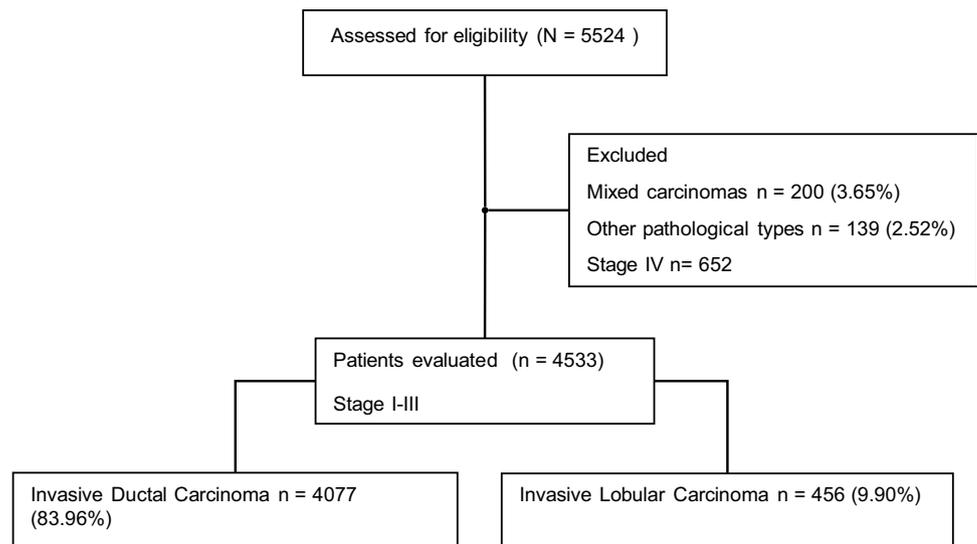
radiotherapy, or with regards to the use of tamoxifen and aromatase inhibitors, as shown in Table 2. In contrast, there was a difference in the percentage of patients who received chemotherapy between both groups (72% for ILC vs. 80% for IDC, $p < 0.001$). We compared the use of chemotherapy between the ILC and IDC groups by clinical stage: for stage II, 69% versus 79% ($p = 0.074$) were prescribed chemotherapy; as for stage IIIC, 93% vs. 97% ($p = 0.004$) were treated with systemic cytotoxic treatment.

Moreover, we analyzed the number of recurrence events by clinical stage in both histologic types. We found no significant difference between them in stage II [IDC 155 (8.9%) vs. ILC 24 (12.70%), $p = 0.55$] and stage III [IDC 467 (28.83%) vs. ILC 61 (34.27%), $p = 0.38$], respectively. Furthermore, complete pathological response was higher in IDC than in ILC. DFS at 5 years for IDC was 80.8% versus 76.2% for ILC. 5-year OS was 88.7% for IDC versus 84.3% for ILC. Both are presented according to characteristics in Table 3. DFS and OS curves are shown in Fig. 2.

Factors that negatively affected the 5-year DFS in multivariate analysis were: clinical stage III (HR 4.2, 95% CI 3.36–5.35; $p < 0.001$), triple negative phenotype (HR 1.4, 95% CI 1.08–1.81; $p = 0.009$), Ki67 $\geq$ 18 (HR 1.6, 95% CI 1.28–2.11; $p < 0.001$) and lobular histological subtype (HR 1.6, 95% CI 1.09–2.49; $p = 0.017$). Factors that negatively influenced OS were: clinical stage III (HR 4.5, 95% CI 3.15–6.54; $p < 0.001$), triple negative phenotype (HR 2.4, 95% CI 1.69–3.48; $p < 0.001$), and Ki67 $\geq$ 18% (HR 1.9, 95% CI 1.27–2.92; $p = 0.02$). The analysis for DFS and OS is described in Table 4.

Discussion

As in previous reports, we found that when compared with IDC, ILC BC patients were older, more frequently hormone-sensitive, had lower nuclear grade, had a lower proliferation index, and less HER2+ and triple negative phenotypes [13, 18, 26, 27]. However, despite the good prognostic factors observed in the ILC group, these did not correlate with better OS compared with IDC. Besides, we identified the ILC pathologic subtype as an independent factor that negatively influenced DFS.

Lobular carcinoma is still less common than IDC even though it's rates are reported to be rising faster [6, 7]. In our cohort, we found ILC to have an incidence of 9.9%, similar to that reported in previous publications [8, 20, 28–30]. This low frequency of this histologic type and the different follow-up range in the studies, have limited the knowledge about outcomes, particularly when compared with IDC. Therefore, data on outcomes are still controversial [1, 2, 4, 8].

In this study we recognized that ILC histologic subtype negatively impacted on DFS in a Mexican population with a high incidence of overweight and obese patients and a high rate of locally-advanced disease treated in a real-life clinical context. Like our results, Colleoni et al. concluded in 851 BC patients with ILC that DFS was worse than that of 5707 patients with IDC (HR = 1.27, 95% CI 1.05–1.53; $p = 0.01$). This population was hormone-sensitive and was treated in an adjuvant setting [19]. Adachi et al. compared

Table 1 Clinical and pathological characteristics of breast cancer patients with invasive ductal carcinoma and invasive lobular carcinoma at National Cancer Institute Mexico, during 2006–2016

Characteristics	Histological types		
	Ductal ($n=4077$) n (%)	Lobular ($n=456$) n (%)	p-values*
Age (years)			
19–39	644 (15.8)	43 (9.4)	
40–64	2835 (69.5)	322 (70.6)	
$\geq$ 65	598 (14.7)	91 (20.0)	< 0.001
Body mass index			
Normal	1114 (27.3)	126 (27.6)	
Overweight/ obesity	2952 (72.4)	328 (71.9)	0.872
No data	11 (0.3)	2 (0.4)	
Hormonal status			
Post-menopausal	2340 (57.4)	290 (63.6)	
Premenopausal	1737 (42.6)	166 (36.4)	0.011
Diabetes			
No	3086 (75.7)	346 (75.9)	
Yes	540 (13.2)	51 (11.2)	0.274
No data	451 (11.1)	59 (12.9)	
Clinical stages			
I–II	2434 (59.7)	274 (60.1)	
III	1643 (40.3)	182 (39.9)	0.873
Nuclear grades			
Low	469 (11.5)	266 (58.3)	
Intermediate/ high	3488 (85.6)	126 (27.7)	< 0.001
No data	120 (2.9)	64 (14.0)	
Phenotypes			
Hormone-sensitive	2371 (58.2)	372 (81.6)	
Triple negative	738 (18.1)	41 (9.0)	
HER2+	926 (22.7)	41 (9.0)	< 0.001
No data	42 (1.0)	2 (0.4)	
Ki67			
$\leq$ 18%	1206 (29.6)	188 (41.2)	
> 18%	1569 (38.5)	109 (23.9)	< 0.001
No data	1302 (31.9)	159 (34.9)	

*χ^2 Analysis

104 luminal ILC patients with 1661 luminal IDC patients, and reported that ILC pathological subtype was related to a high-risk of recurrence (HR = 2.49, 95% CI 1.28–4.85; $p = 0.009$) [18]. These results contrast with Silverstein et al., who found a better DFS for ILC than IDC (74% vs. 63%, $p < 0.03$) or with Viale et al., who concluded the same DFS for both histologic subtypes with a median follow-up of 7.3 years [15, 17, 31].

Table 2 Treatment characteristics of breast cancer patients with invasive ductal and invasive lobular carcinoma at National Cancer Institute Mexico during 2006–2016

Treatment modality	Histological types		p-values*
	Ductal ($n=4077$) n (%)	Lobular ($n=456$) n (%)	
Chemotherapy			
No	831 (20.4)	129 (28.3)	
Yes	3242 (79.5)	326 (71.5)	< 0.001
Not data	4 (0.1)	1 (0.2)	
Pathological responses			
Complete	703 (17.2)	46 (10.1)	
Residual disease	940 (23.1)	129 (28.3)	< 0.001
Not undergo	2434 (59.7)	281 (61.6)	
Endocrine therapy			
Tamoxifen	1549 (38.0)	205 (45.0)	
Aromatase inhibitors	1266 (31.1)	183 (40.1)	0.416
Radiotherapy			
No	1449 (35.5)	156 (34.2)	
Yes	2618 (64.2)	299 (65.6)	0.594
No data	10 (0.3)	1 (0.2)	
Surgery types			
Conservative	794 (19.5)	87 (19.1)	
Radical	3008 (73.8)	339 (74.3)	0.824
No data	275 (6.7)	30 (6.6)	

*χ^2 Analysis

Regarding OS, we did not find the ILC pathologic subtype to be an independent prognostic factor. Our short median follow-up of 39 months might explain this finding. In this regard, data on OS have been conflicting. Several studies had reported similar or better OS for ILC compared with IDC [4, 15, 16, 26, 31]. Nevertheless, other reports have shown that ILC negatively influences OS [1, 18, 19]. Chen et al. found that OS depended on the length of follow-up: before 60 months, the ILC group had better OS than IDC (HR 1.118, $p < 0.0001$); however, after 5 years, there was a shift for better OS in the IDC group (HR 0.775, $p < 0.0001$) [1].

The significant difference in DFS and OS for women with less than 40 years old between IDC and ILC report in Table 3, probably is influenced by the fact that most of our patients received tamoxifen because this was the standard of care at that time. Also, these findings correlated with our previous report by Villarreal-Garza et al., where patients with less than 40 years had worst OS particularly in the luminal B phenotype [3].

We hypothesized that these contrasting results are related to the prevalent retrospective nature of the reports, size of the population included, clinical stages involved, time of follow-up, oncological treatments used, lack of information on hormone-receptors, HER2 status, and different

Table 3 Five-year overall survival and disease-free survival of breast cancer patients with invasive ductal and lobular carcinoma at National Cancer Institute Mexico during 2006–2016

Variables	DFS			OS		
	Ductal (%)	Lobular (%)	p-values*	Ductal (%)	Lobular (%)	p-values*
Age (years)						
19–39	73.2	54.8	0.042	85.1	71.2	0.044
40–64	82.2	78.7	0.234	89.7	87.1	0.286
≥ 65	82.6	80.3	0.695	87.9	81.6	0.146
Hormonal status						
Post-menopausal	82.1	80.9	0.708	89.8	85.9	0.097
Premenopausal	78.9	69.1	0.022	87.2	81.7	0.143
Body mass index						
Normal	79.8	73.7	0.211	87.4	80.5	0.092
Overweight/obesity	81.2	76.9	0.156	89.3	85.7	0.112
Diabetes						
No	81.8	83.2	0.575	90.1	88.8	0.533
Si	81.1	70.0	0.149	91.0	96.8	0.261
Stages						
I–II	91.2	88.3	0.205	95.5	94.0	0.399
III	65.9	60.6	0.302	78.9	71.9	0.083
Nuclear grades						
Low	90.8	78.7	< 0.001	96.7	89.5	0.001
Intermediate/high	79.5	73.8	0.274	87.5	71.9	< 0.001
Phenotypes						
Hormone-sensitive	83.7	79.7	0.136	91.3	89.4	0.428
Triple negative	69.6	57.6	0.328	77.5	54.2	0.005
HER2+	81.6	62.9	0.014	90.6	74.4	0.004
Ki67						
≤ 18%	88.6	76.6	0.011	95.9	90.1	0.074
> 18%	73.9	67.9	0.415	86.2	85.3	0.812
Pathological responses						
Complete	82.9	74.2	0.264	91.9	88.3	0.492
Residual disease	67.1	66.4	0.941	80.6	80.7	0.935
Endocrine therapy						
Tamoxifen	87.4	83.2	0.226	94.4	93.6	0.744
Aromatase inhibitors	82.9	76.8	0.086	91.4	88.3	0.294
Chemotherapy (ADY/NDY)						
No	95.6	96.2	0.802	96.4	95.9	0.841
Yes	77.5	71.8	0.063	87.0	82.5	0.065

*Contrast survival test

characteristics used in the multivariate analysis models [1, 8, 10, 15–19, 26, 31]. In our multivariate model, we included age, overweight/obesity, clinical stage, phenotype by immunohistochemistry, nuclear grade, and Ki67.

We need to consider that in our real-world data, all post-menopausal patients with ILC did not use aromatase inhibitors as adjuvant treatment. However, in the univariate analysis, this variable was not significantly related to DFS or OS. Additionally, the percentage of patients that did not receive chemotherapy in the locally-advanced disease setting was lower for ILC than for IDC. Nevertheless, this issue was not

associated with a greater recurrence risk by pathological subtype or found to influence OS.

As in other publications, we propose that ILC histology should be considered differently as used to, in light of the finding that it's pathological characteristics, traditionally associated with a good prognosis, do not seem to impact on OS in a positive way [1, 18, 32]. ILC is increasingly recognized as having a different biology, with the identification of alterations such as the loss of E-cadherin in 90%, the incidence of cathepsin D (86%), *FOXA1* mutations (3.7%), PTEN inactivation, *Akt*
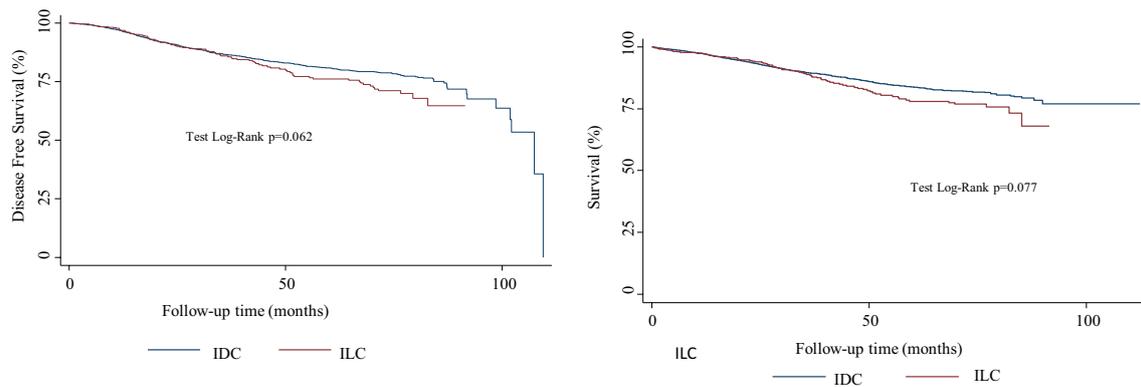
Fig. 2 Disease-free survival curves (left) and overall survival curves (right) for patients with invasive lobular carcinoma and invasive ductal carcinoma at National Cancer Institute during 2006–2016

Table 4 Multivariate disease-free survival analysis by histologic type and other prognosis factors in breast cancer patients with invasive ductal and lobular carcinoma at National Cancer Institute Mexico during 2006–2016

Variables	DFS			OS		
	HR[a]	95% CI	p	HR[a]	95% CI	p
Clinical stages						
I–II	1.0			1.0		
III	4.2	3.36–5.35	< 0.001	4.5	3.15–6.54	< 0.001
Phenotypes						
Hormone-sensitive	1.0			1.0		
Triple negative	1.4	1.08–1.81	0.009	2.4	1.69–3.48	< 0.001
HER2+	0.9	0.70–1.17	0.465	0.9	0.62–1.41	0.753
Nuclear grades						
Low	1.0			1.0		
Intermediate/high	1.4	0.92–2.04	0.111	1.2	0.64–2.35	0.521
Ki67						
< 18	1.0			1.0		
≥ 18	1.6	1.28–2.11	< 0.001	1.9	1.27–2.92	0.02
Histological types						
Ductal	1.0			1.0		
Lobular	1.6	1.09–2.49	0.017	1.1	0.56–2.35	0.694

[a]HR adjusted for age and the variables presented in the model

activation, and variation in Bcl-2 (89%), among other recently reported molecular features [7, 12, 17, 32, 33].

So far, research and treatments specifically directed at this population are scarce. For this reason, we encourage research in this field. We are aware that, as a retrospective report, it is difficult to get on statements. Nonetheless, it is important to keep in mind that lobular invasive breast carcinoma seems to be a different disease. These data will help us move forward in the search of an individualized treatment according to the behavior of ILC.

Conclusions

Our results contribute to the current data on ILC, confirming its different biological behavior and less favorable long-term prognosis in terms of DFS than previously reported. As far as we know, this is the first report in a Hispanic population.

Compliance with ethical standards

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