

Mixed Invasive Ductal and Lobular Carcinoma of the Breast: Prognosis and the Importance of Histologic Grade

OTTO METZGER-FILHO,^{a,†} ARLINDO R. FERREIRA^{ⓑ, a,b,†}, RINATH JESELSON,^a WILLIAM T. BARRY,^a DEBORAH A. DILLON,^a JANE E. BROCK,^a INES VAZ-LUIS,^a MELISSA E. HUGHES,^a ERIC P. WINER,^a NANCY U. LIN^a

^aDana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, Massachusetts, USA; ^bHospital de Santa Maria and Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

[†]Contributed equally.

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast cancer, early • Carcinoma, lobular • Invasive ductal carcinoma, breast • Tumor grading • Outcomes research

ABSTRACT

Background. The diagnosis of mixed invasive ductal and lobular carcinoma (IDC-L) in clinical practice is often associated with uncertainty related to its prognosis and response to systemic therapies. With the increasing recognition of invasive lobular carcinoma (ILC) as a distinct disease subtype, questions surrounding IDC-L become even more relevant. In this study, we took advantage of a detailed clinical database to compare IDC-L and ILC regarding clinicopathologic and treatment characteristics, prognostic power of histologic grade, and survival outcomes.

Materials and Methods. In this retrospective cohort study, we identified 811 patients diagnosed with early-stage breast cancer with IDC-L or ILC. Descriptive statistics were performed to compare baseline clinicopathologic characteristics and treatments. Survival rates were subsequently analyzed using the Kaplan–Meier method and compared using the Cox proportional hazards model.

Results. Patients with ILC had more commonly multifocal disease, low to intermediate histologic grade, and HER2-negative disease. Histologic grade was prognostic for patients with IDC-L but had no significant discriminatory power in patients with ILC. Among postmenopausal women, those with IDC-L had significantly better outcomes when compared with those with ILC: disease-free survival (DFS) and overall survival (OS; adjusted hazard ratio [HR], 0.54; 95% confidence interval [CI] 0.31–0.95). Finally, postmenopausal women treated with an aromatase inhibitor had more favorable DFS and OS than those treated with tamoxifen only (OS adjusted HR, 0.50; 95% CI, 0.29–0.87), which was similar for both histologic types ($p = .212$).

Conclusion. IDC-L tumors have a better prognosis than ILC tumors, particularly among postmenopausal women. Histologic grade is an important prognostic factor in IDC-L but not in ILC. *The Oncologist* 2019;24:e441–e449

Implications for Practice: This study compared mixed invasive ductal and lobular carcinoma (IDC-L) with invasive lobular carcinomas (ILCs) to assess the overall prognosis, the prognostic role of histologic grade, and response to systemic therapy. It was found that patients with IDC-L tumors have a better prognosis than ILC, particularly among postmenopausal women, which may impact follow-up strategies. Moreover, although histologic grade failed to stratify the risk of ILC, it showed an important prognostic power in IDC-L, thus highlighting its clinical utility to guide treatment decisions of IDC-L. Finally, the disease-free survival advantage of adjuvant aromatase inhibitors over tamoxifen in ILC was consistent in IDC-L.

INTRODUCTION

Breast cancer is morphologically classified as either invasive breast carcinoma of no special type (NST), also known as invasive ductal carcinoma (IDC), or as a “special subtype” of breast cancer [1]. Special subtypes account for an array

of different histological features, with invasive lobular carcinoma (ILC) being the most common subtype [2]. In addition, certain breast carcinomas present with varying proportions of NST and other types of breast cancers and

Correspondence: Otto Metzger-Filho, M.D., 450 Brookline Avenue Yawkey 1238, Boston, Massachusetts 02215, USA. Telephone: 617-763-3110; email: otto_metzger@dfci.harvard.edu Received June 19, 2018; accepted for publication August 31, 2018; published Online First on December 5, 2018. <http://dx.doi.org/10.1634/theoncologist.2018-0363>

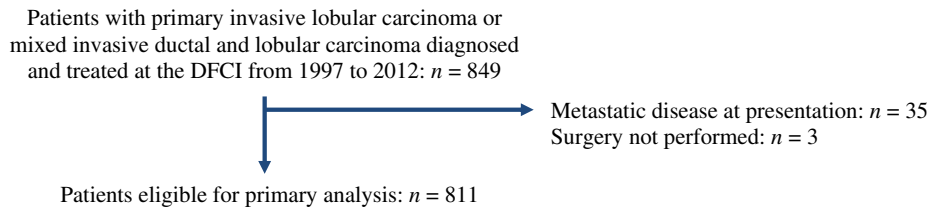


Figure 1. Study Consort diagram.
Abbreviation: DFCI, Dana-Farber Cancer Institute.

are classified as *carcinomas of mixed type*. This category is defined as tumors in which at least 50% of the tumor has a specialized pattern and 10%–49% of the tumor has a non-specialized pattern [1]. Mixed invasive ductal and lobular carcinomas (IDC-Ls) account for approximately 5% of all breast cancers and, together with ILC, present a growing incidence [2–4].

ILC has long been distinguished from other types of breast cancer for its unique clinicopathologic features and, more recently, genomic landscape [5–7]. When compared with IDC, ILC tends to lack the cell adhesion molecule e-cadherin, is more frequently multifocal, is hormone receptor-positive/HER2-negative, is lower grade (I or II), presents reduced response rates to preoperative chemotherapy, and may benefit differently from adjuvant endocrine therapies [8–11]. In contrast, studies characterizing IDC-L are currently scarce and limited by cohort size, lack of granular clinicopathological/treatment data, or short follow-up [2, 12–16]. It is thus unclear how patients with these tumors perform in terms of survival outcomes and whether known classic prognostic features of IDC, such as histologic grade, apply to IDC-L.

In this retrospective analysis, we took advantage of a large, detailed, and curated single center database to compare clinicopathologic features and outcomes between ILC and IDC-L. We further focused on the prognostic implications of histological grade, taking into consideration differences in systemic therapies.

SUBJECTS, MATERIALS, AND METHODS

Study Design and Data Source

This is a retrospective cohort study using prospectively collected data from the Dana-Farber Cancer Institute (DFCI) and stored in the National Comprehensive Cancer Network Oncology Outcomes Database. The current study was approved by the DFCI Institutional Review Board and complies with all national regulations. We applied the STROBE statement in reports of cohort studies (<http://www.strobe-statement.org/>).

Patient Selection and Extracted Information

We identified all patients who were older than 18 years of age and were diagnosed and treated at DFCI for stage I–III breast cancer of ILC or IDC-L histology from 1997 to 2007. IDC-L was defined as tumors in which at least 50% of the tumor is of lobular pattern and 10%–49% is of nonspecialized pattern. Follow-up details (disease recurrence, new primaries, and death) were available up to January 2012

and analyzed as per registry specifications. Dates of study entry were balanced between groups. We excluded patients with metastatic disease at presentation, patients who received neoadjuvant therapy, patients who did not have surgery, and patients with other concurrent primary tumors. A cohort of 811 patients was identified for the analysis (Fig. 1).

Overall survival (OS), disease-free survival (DFS), and time to specific relapse were defined as time from diagnosis to death, time from diagnosis to any relapse or death, and time from diagnosis to local, regional, or distant relapse, respectively.

Statistical Analysis

Descriptive statistics of baseline demographic, clinicopathologic, and treatment characteristics were performed. Differences between groups were tested using chi-squared test or *t* test where applicable. Time-to-event data were analyzed using the Kaplan–Meier method and compared using Cox proportional hazards models. All patients with missing data in relevant variables were excluded from the multivariate analysis. All the presented analyses successfully met proportional hazards assumption as assessed by the Schoenfeld residuals. Missing information was considered as missing at random, as per study design. The analyses were completed using Stata 12.3 (StataCorp LP; College Station, TX).

RESULTS

Study Population and Baseline Characteristics

The study population included 811 patients, 337 (41.6%) with ILC and 474 (58.4%) with IDC-L (Table 1). When compared with patients with IDC-L, patients with ILC were slightly older and had larger tumors (11.0% had tumors >5 cm vs. 3.0% for IDC-L; $p < .001$), more positive nodes (16.9% had ≥ 4 nodes vs. 9.7% for IDC-L; $p = .002$), and less frequent poorly differentiated tumors (8.3% vs. 19.8% for IDC-L; $p < .001$). In addition, ILC was less likely to be HER2 positive (3.9% vs. 8.6%; $p = .02$). Finally, multifocal disease was also more common in patients with ILC (36.2% vs. 26.6%; $p = .004$).

Treatment

Patients with ILC underwent mastectomy more frequently than those with IDC-L (57.0% vs. 46.8%; $p = .004$; Table 1). Yet no significant differences were found in the frequency of radiotherapy (69.1% vs. 72.6% for IDC-L; $p = .287$). Nevertheless, despite the higher tumor burden at diagnosis,

Table 1. Patient demographics, clinicopathologic characteristics, and treatments overall and by histologic type

Variable list	Total sample (n = 811)	ILC (n = 337)	IDC-L (n = 474)	p value (ILC vs. IDC-L)
Demographic and clinicopathologic characteristics				
Median age (IQR), yr	53.79 (46.90–62.16)	54.55 (47.85–64.17)	53.02 (46.17–60.97)	.030
Menopausal status, n (%)				.084
Premenopausal	349 (43.0)	133 (39.5)	216 (45.6)	
Postmenopausal	462 (57.0)	204 (60.5)	258 (54.4)	
Multifocal tumor (in pathology report), n (%)				.004
Present	248 (30.5)	122 (36.2)	126 (26.6)	
Missing	66 (8.1)	26 (7.7)	40 (8.4)	
pT (tumor size, pathological), n (%)				<.001
≤2 cm	482 (59.4)	184 (54.6)	298 (62.9)	
>2–5 cm	200 (24.7)	89 (26.4)	111 (23.4)	
>5 cm	51 (6.3)	37 (11.0)	14 (3.0)	
Missing	78 (9.6)	27 (8.0)	51 (10.7)	
Dissected nodes, median (range)	9 (3–15)	10 (4–15)	9 (3–14)	.235
Positive nodes, n (%)				.002
Negative	408 (50.3)	174 (51.6)	234 (49.4)	
1–3 positive	198 (24.4)	67 (19.9)	131 (27.6)	
4–9 positive	66 (8.1)	33 (9.8)	33 (7.0)	
10 or more	37 (4.6)	24 (7.1)	13 (2.7)	
Missing	102 (12.6)	39 (11.6)	63 (13.3)	
Simplified TNM staging, n (%)				.026
Stage I	351 (43.2)	144 (42.7)	207 (43.7)	
Stage II	355 (43.8)	137 (40.7)	218 (46.0)	
Stage III	105 (13.0)	56 (16.6)	49 (10.3)	
Lymphovascular invasion, n (%)				<.001
Yes	219 (27.0)	55 (16.3)	164 (34.6)	
No	592 (73.0)	282 (83.7)	310 (65.4)	
Histologic grade, n (%)				<.001
Grade I	182 (22.4)	113 (33.5)	69 (14.6)	
Grade II	497 (61.3)	188 (55.8)	309 (65.2)	
Grade III	122 (15.1)	28 (8.3)	94 (19.8)	
Missing	10 (1.2)	8 (2.4)	2 (0.4)	
Hormone receptor, n (%)				.548
ER and/or PR positive	776 (95.7)	323 (95.9)	453 (95.6)	
ER and PR negative	33 (4.1)	12 (3.5)	21 (4.4)	
Missing	2 (0.2)	2 (0.6)	0 (0)	
ER positive only	771 (95.1)	321 (95.3)	450 (94.9)	.558
HER2 receptor, n (%)				.02
Positive	54 (6.7)	13 (3.9)	41 (8.6)	
Negative	680 (83.8)	273 (81.0)	407 (85.9)	
Missing	77 (9.5)	51 (15.1)	26 (5.5)	
Molecular type, n (%)				.01
ER or PR+ and HER2–	659 (81.3)	268 (79.5)	391 (82.5)	
ER or PR+ and HER2+	44 (5.4)	8 (2.4)	36 (7.6)	
ER– and PR– and HER2+	10 (1.2)	5 (1.5)	5 (1.0)	
ER– and PR– and HER2–	21 (2.6)	5 (1.5)	16 (3.4)	
Missing	77 (9.5)	51 (15.1)	26 (5.5)	

(continued)

Table 1. (continued)

Variable list	Total sample (n = 811)	ILC (n = 337)	IDC-L (n = 474)	p value (ILC vs. IDC-L)
Treatment characteristics				
Surgery, n (%)				.004
Mastectomy	414 (51.0)	192 (57.0)	222 (46.8)	
Breast conservation	397 (49.0)	145 (43.0)	252 (53.2)	
Radiotherapy, n (%)				.287
Yes	577 (71.2)	233 (69.1)	344 (72.6)	
No	234 (28.8)	104 (30.9)	130 (27.4)	
Adjuvant endocrine therapy, n (%)				.371
Yes	722 (89.0)	302 (89.6)	420 (88.6)	
No	56 (6.9)	20 (5.9)	36 (7.6)	
Missing	33 (4.1)	15 (4.5)	18 (3.8)	
Adjuvant chemotherapy, n (%)				.021
Yes	451 (55.6)	170 (50.5)	281 (59.3)	
No	306 (37.7)	141 (41.8)	165 (34.8)	
Missing	54 (6.7)	26 (7.7)	28 (5.9)	

Bold highlights the *p* values crossing the .05 mark toward statistical significance.

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC-L, mixed invasive ductal and lobular carcinoma; ILC, invasive lobular carcinoma; IQR, interquartile range; PR, progesterone receptor.

patients with ILC received chemotherapy less frequently (50.5% vs. 59.3% for IDC-L; *p* = .021).

Outcomes

The median follow-up for the entire cohort was 7.9 years and was similar for both histologic types (*p* = .190). Among 337 patients with ILC, 73 (21.7%) developed a DFS event and 62 (18.4%) developed an OS event, whereas among 474 patients with IDC-L, 70 (14.8%) developed a DFS event and 59 (12.5%) developed an OS event. For patients with ILC, the 5- and 10-year proportion of patients free of a DFS event was 89.3% (95% confidence interval [CI], 85.3–92.2) and 74.2% (95% CI, 67.8–79.6), respectively, whereas for IDC-L, the 5- and 10-year rates were 90.4% (95% CI, 87.3–92.8) and 81.0% (95% CI, 75.7–85.3), respectively.

In a multivariate model, variables associated with DFS included year of diagnosis, TNM stage, and histologic grade, whereas variables associated with OS included age at diagnosis, TNM staging, and histologic grade (Table 2). Overall, the differences in DFS and OS outcomes by histologic type were not statistically significant, despite a trend towards an improved outcome for IDC-L when compared with ILC. Specifically, the hazard ratio for DFS was 0.72 (95% CI, 0.49–1.08; *p* = .114; Table 2; Fig. 2) and the hazard ratio for OS was 0.77 (95% CI, 0.50–1.20; *p* = .244; Table 2; supplemental online Fig. 1).

Given the hormone dependent nature of lobular carcinomas, we tested whether menopausal status modified outcomes according to histologic type. The interaction between histology and menopausal status was statistically significant for OS, and a trend in the same direction was noted for DFS (Table 2). When stratifying the analysis by menopausal status, no difference in DFS or OS was seen in premenopausal patients (adjusted hazard ratio [HR] for DFS, 1.06; 95% CI, 0.52–2.17; *p* = .875), but superior

outcome is evident for postmenopausal patients with IDC-L compared with ILC (adjusted HR for DFS, 0.58; 95% CI, 0.34–0.97; *p* = .039; Fig. 3; supplemental online Fig. 2).

To explore the prognostic role of histologic grade, we performed an interaction analysis between histology and grade, which was statistically significant (Table 2). Although histologic grade was unable to discriminate the prognosis of patients with ILC, it was an effective tool to discriminate the prognosis of those with IDC-L (Fig. 4; supplemental online Fig. 3).

We further explored the relative effectiveness of tamoxifen versus aromatase inhibitor (AI) among postmenopausal patients with hormone receptor-positive tumors. Patients treated with an AI (as monotherapy or sequentially with tamoxifen) had more favorable outcomes than those treated with tamoxifen only, both in terms of DFS (HR, 0.36; 95% CI, 0.21–0.61; *p* < .001) and OS (HR, 0.50; 95% CI, 0.29–0.87; *p* = .015; supplemental online Table 1). The magnitude of benefit was similar for both histologic types (*p* = .212). Similar results for both analyses were obtained after the introduction of a landmark analysis including only patients free of recurrence at 24 months (which would be a reasonable date of endocrine therapy switch from tamoxifen to an AI in clinical practice).

Disease Recurrence

A total of 91 patients had a disease recurrence: 44 (48.35%) patients with ILC and 47 (51.65%) patients with IDC-L (*p* = .163; supplemental online Table 2). When considering the specific site of disease recurrence, bone was the most frequent site in both histologic types (14 [37.84%] vs. 17 cases [53.12%] for ILC and IDC-L, respectively). Nevertheless, intra-abdominal recurrences (excluding liver) were only identified in ILC (7 [18.9%]).

Table 2. Multivariate Cox proportional hazards model for overall survival and disease-free survival

Variable list	Disease-free survival (No. patients 681/811; events 110/143)		Overall survival (No. patients 681/811; events 93/121)	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Main multivariate model (estimates without interaction terms)				
ILC (vs. IDC-L)	0.72 (0.49–1.08)	.114	0.77 (0.50–1.20)	.244
Age at diagnosis (per year increase)	1.01 (0.99–1.04)	.091	1.03 (1.00–1.06)	.034
Menopausal status	1.08 (0.60–1.96)	.791	1.14 (0.59–2.21)	.703
TNM staging				
Stage I	(reference)	(reference)	(reference)	(reference)
Stage II	2.43 (1.37–4.31)	.002	2.309 (1.213–4.393)	.011
Stage III	13.57 (6.71–27.44)	<.001	12.117 (5.714–25.698)	<.001
Lymphovascular invasion	1.06 (0.67–2.11)	.815	1.18 (0.72–1.93)	.519
Histologic grade				
Grade I	(reference)	(reference)	(reference)	(reference)
Grade II	1.24 (0.73–2.12)	.423	1.639 (0.879–3.057)	.120
Grade III	2.20 (1.14–4.23)	.018	2.450 (1.138–5.276)	.022
ER positive	0.70 (0.22–2.22)	.543	0.46 (0.13–1.59)	.222
HER2 receptor positive	0.76 (0.39–1.46)	.406	0.96 (0.49–1.88)	.906
Adjuvant chemotherapy use	0.66 (0.37–1.17)	.159	0.87 (0.46–1.65)	.673
Adjuvant hormone therapy use	0.58 (0.18–1.84)	.360	0.72 (0.20–2.57)	.613
Year of diagnosis	0.91 (0.83–0.99)	.034	1.04 (0.93–1.16)	.489
Interaction term 1 in the main multivariate model (see accompanying Fig. 3)				
Histologic type and menopausal status	0.52	.118	0.31	.020
Premenopausal				
ILC	(reference)	(reference)	(reference)	(reference)
IDC-L	1.06 (0.52–2.17)	.875	1.52 (0.62–3.74)	.356
Postmenopausal				
ILC	(reference)	(reference)	(reference)	(reference)
IDC-L	0.58 (0.34–0.97)	.039	0.53 (0.30–0.94)	.028
Interaction term 2 in the main multivariate model (see accompanying Fig. 4)				
Histologic type and grade	2.08	.022	2.11	.033
ILC				
Grade I	(reference)	(reference)	(reference)	(reference)
Grade II	1.06 (0.57–1.97)	.859	1.17 (0.58–2.35)	.660
Grade III	1.27 (0.44–3.64)	.657	1.07 (0.32–3.49)	.917
IDC-L				
Grade I	(reference)	(reference)	(reference)	(reference)
Grade II	2.34 (0.70–7.80)	.166	6.26 (0.84–46.76)	.074
Grade III	5.65 (1.58–20.2)	.008	11.36 (1.44–89.90)	.021

Bold highlights the *p* values crossing the .05 mark toward statistical significance.

Abbreviations: CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDC-L, mixed invasive ductal and lobular carcinoma; ILC, invasive lobular carcinoma.

Finally, using a multivariate analysis model (controlling for the same variables detailed in Table 2), we found no significant differences according to histologic type for other outcomes, namely locoregional recurrence (HR, 0.97; 95% CI, 0.36–2.60; *p* = .944), distant recurrence (HR, 0.69; 95% CI, 0.41–1.18; *p* = .174), bone recurrence (HR, 0.80; 95% CI, 0.35–1.80; *p* = .584), and second breast cancers (HR, 1.81; 95% CI, 0.65–5.05; *p* = .258).

DISCUSSION

In this retrospective analysis, we took advantage of a clinical database including 811 patients to compare clinicopathologic features, management, and survival outcomes between IDC-L and ILC. Patients with ILC were older, had more multifocal disease, larger tumors, more positive nodes, and more HER2-negative tumors, and received less frequent adjuvant chemotherapy than patients with IDC-L. When compared

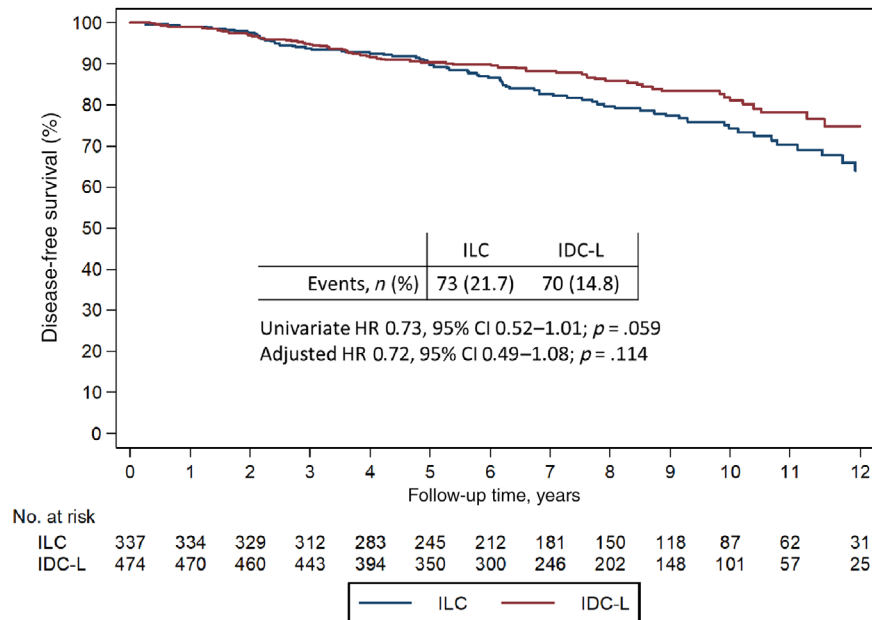


Figure 2. Disease-free survival in ILC and IDC-L.

Abbreviations: CI, confidence interval; IDC-L, mixed invasive ductal and lobular carcinoma; ILC, invasive lobular carcinoma; HR, hazard ratio.

with ILC, IDC-L had superior survival outcomes, particularly for women in the postmenopausal setting. Histologic grade was an important prognostic factor for IDC-L but not for ILC. These observations resemble differences between hormone receptor-positive IDC and ILC [12, 17–19].

Previous retrospective studies have failed to identify meaningful differences in survival outcomes in patients with ILC compared with patients with IDC-L [13–16, 20, 21]. By contrast, in a retrospective series including 140 patients with IDC-L, Rakha et al. reported worse outcomes for patients with IDC-L than for those with ILC ($n = 380$) [12]. The interpretation of previous results is impaired by cohort size, limited multivariate adjustment, or short follow-up. In this study, the overall results suggested similar survival outcomes between patients with ILC and IDC-L, but when stratifying by menopausal status, we noticed superior survival outcomes for patients with IDC-L. These observations were corroborated by a large analysis of the Surveillance, Epidemiology, and End Results (SEER) database, including a total of 209,109 patients [22]. In the SEER analysis, Xiao et al. compared survival outcomes based on histology, including 172,379 patients with IDC, 17,503 patients with ILC, and 19,227 patients with IDC-L. The survival analysis performed pointed to better breast cancer-specific survival for patients with IDC-L than with IDC and ILC. The evaluation of HR over time using scaled Schoenfeld residual plots revealed interesting findings; the HR of IDC-L versus IDC increased over time, indicating a continuous long-term risk of relapse, which could be attributed to the lobular component of mixed tumors. By contrast, the HR for the comparison of IDC-L versus ILC decreased over time, indicating better long-term prognosis for IDC-L versus ILC. When evaluating the differences in outcomes between IDC-L and ILC, patients aged >50 years diagnosed with IDC-L had superior outcomes [22]. Although

the larger sample size from the SEER analysis provided robust prognostic information, the lack of detailed clinicopathologic information (e.g. HER2 status) and treatment information is an important limitation.

Our results complement the findings from the SEER analysis, given that we were able to interpret survival outcomes correcting for important clinicopathologic variables (e.g., adjuvant systemic therapy). Taken together, available data suggests that patients diagnosed with IDC-L have a better survival outcome when compared with patients with ILC, which is probably explained by the continuous long-term risk of relapse associated with ILC. Furthermore, patients with IDC-L generally did not develop intra-abdominal relapses that characterize ILC. The Cancer Genome Atlas (TCGA) research network recently published results of genomic characterization of 490 IDC, 127 ILC, 88 IDC-L, and 112 other breast cancer cases [23]. As expected, ILC-like tumors were enriched for luminal A subtype, *CDH1* mutations, and loss of e-cadherin by mRNA expression. Among the 88 cases of IDC-L, there did not appear to be a distinct genomic profile; rather, the IDC-L cases segregated into IDC-like ($n = 64$) or ILC-like ($n = 24$) tumors. The overrepresentation of molecular IDC-like tumors in the clinical IDC-L cases in the TCGA is consistent with our findings—IDC-L (as assessed by pathological evaluation) diverged from ILC in histologic grade, frequency of HER2 status, and survival outcomes, among other differences, which would be expected if most clinical IDC-Ls are molecular IDC-like. Further research is needed to investigate whether there is any clinical utility of molecularly classifying IDC-L for the purpose of prognostic evaluation and/or treatment planning.

In our cohort, histologic grade was prognostic for IDC-L but not for ILC. In a previous retrospective series pooling outcomes from 707 classic ILCs, 102 special subtypes of

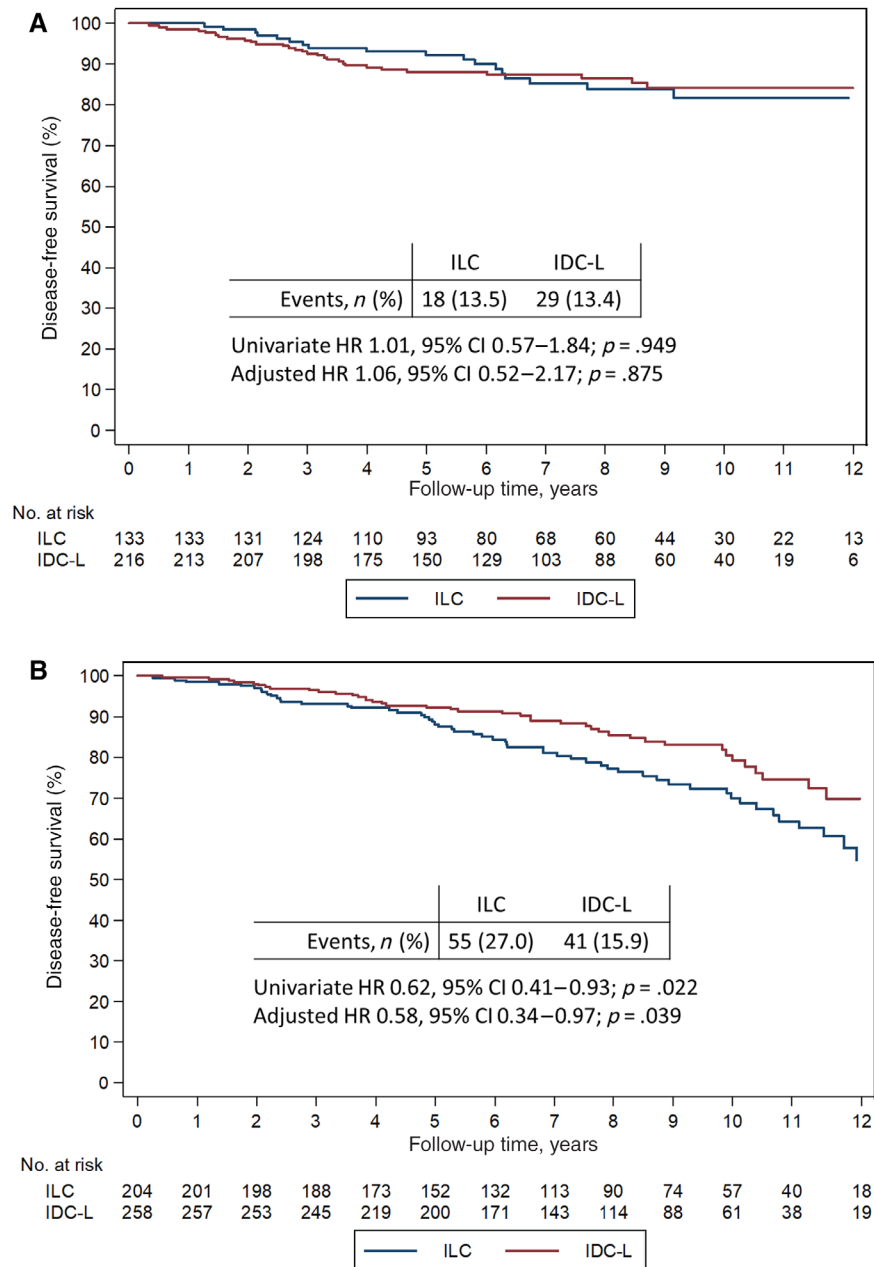


Figure 3. Disease-free survival in ILC and IDC-L. Disease-free survival in premenopausal (A) and postmenopausal (B) patients. Abbreviations: CI, confidence interval; IDC-L, mixed invasive ductal and lobular carcinoma; ILC, invasive lobular carcinoma; HR, hazard ratio.

ILC, and 44 mixed tumors, Talman et al. found a significant difference in OS and DFS between grade II and III tumors but not between grade I and II tumors [24]. In addition, a subsequent study including 517 patients with ILC [25] reported a significant prognostic value for histologic grade. However, approximately one third of cases in the series were special subtypes of ILC often characterized by tubule formation, and when tubule formation was removed from the analysis, the remaining histologic grade variables (i.e., mitotic count and nuclear pleomorphism) were no longer associated with outcome. Collectively, our findings and those of others suggest that the current grading system may be limited for ILC but useful for IDC-L.

In an exploratory analysis from our cohort, postmenopausal patients receiving adjuvant AI, either as monotherapy or sequentially after tamoxifen, had better outcomes when compared with patients treated with tamoxifen monotherapy independently of the histologic subtype. These results are in agreement with the updated AI overview meta-analysis [26]. Of interest, two retrospective studies have compared the effectiveness of AI versus tamoxifen among patients diagnosed with ILC or IDC: the BIG1-98 study and the ABCSG-8 study [10, 11]. In the BIG1-98 study, patients with ILC derived a greater benefit with letrozole when compared with tamoxifen [10], and in the ABCSG-8 study, patients diagnosed with ILC had better

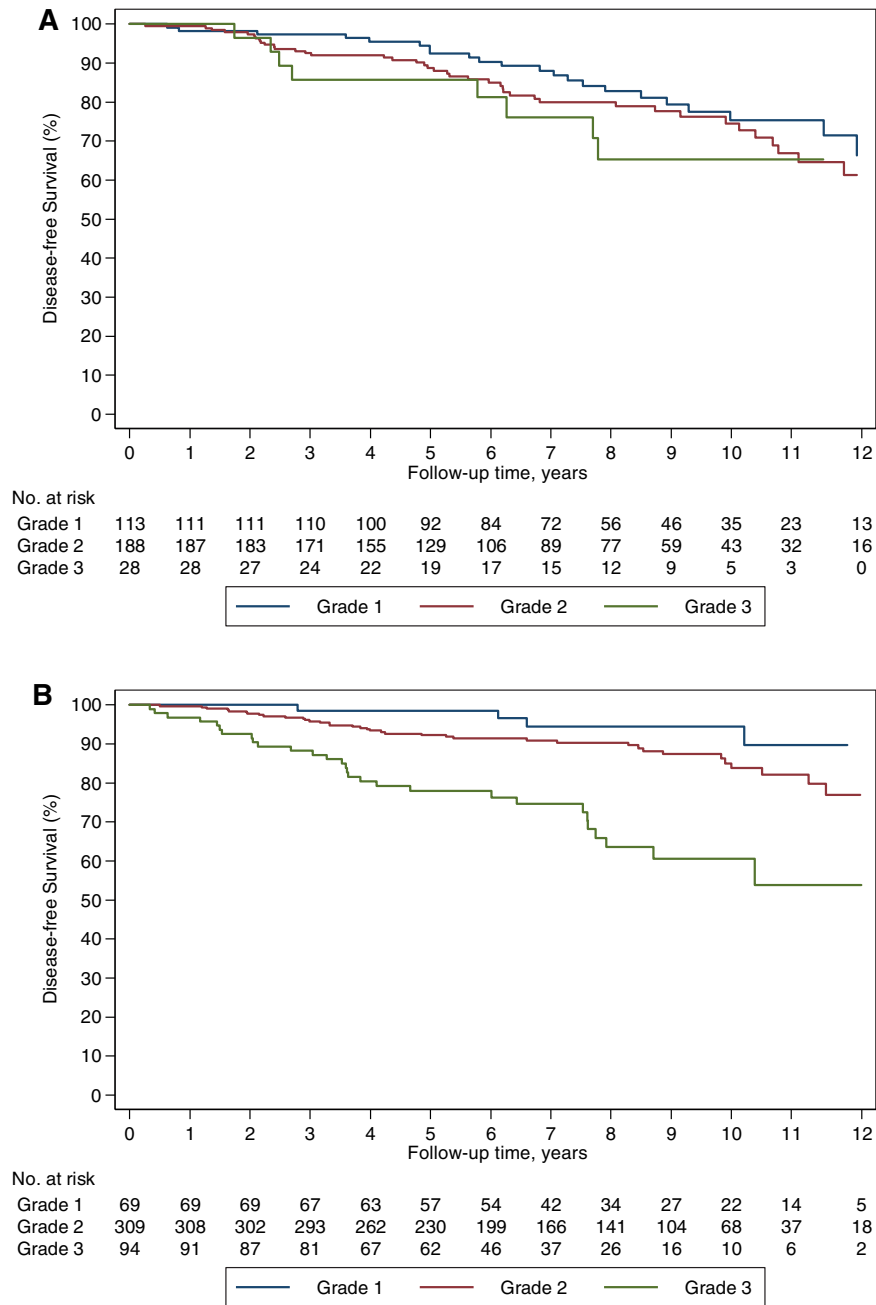


Figure 4. Disease-free survival based on tumor grade. Disease-free survival in ILC (A) and IDC-L (B).

survival outcomes when treated with a sequential regimen (tamoxifen-AI) than with tamoxifen monotherapy [11] Our current study is limited in its ability to determine a difference between AI and tamoxifen for patients diagnosed with ILC and IDC-L, and further investigation into this topic is needed.

We acknowledge a number of limitations to study. Despite the methodological rigor, as a retrospective observational study, it is amenable to residual confounding. Although pathologic review was, in most cases, performed by an academic pathologist at Brigham and Women’s Hospital, central pathology review and additional immunohistochemical studies, such as e-cadherin/p120 [27] to further characterize these tumors, were not performed. Tumor classifications were taken from the diagnostic pathology

reports and likely reflect individual pathologist preferences as well as changing tumor classification practices over the period of this study. Finally, the relative effectiveness of tamoxifen versus AI results is based on observational data and not a randomized trial.

CONCLUSION

In this study, we report several important findings: (a) patients diagnosed with IDC-L have a better prognosis than patients with ILC, particularly for postmenopausal women; (b) histologic grade is an imperfect tool for patients with ILC but provides relevant information for patients with IDC-L; and (c) consistent with data from phase III studies, where AIs have shown a DFS advantage

over tamoxifen that appeared greatest in the ILC subset, these improvements also held true for patients with IDC-L. Taken together, our work adds to the literature pointing to significant differences in survival outcomes for patients with IDC-L when compared with patients with ILC. Patients with IDC-L have more favorable outcomes, particularly for those in the postmenopausal setting; the unfavorable outcomes associated with ILC are likely to be explained by its continuous pattern of relapse beyond year 5.

ACKNOWLEDGMENTS

This work was supported by the Susan G. Komen Foundation for the Cure (Grant PDF14302599), Fundação para a Ciência e a Tecnologia (Grant HMSP-ICJ/0007/2013 under the Harvard Medical School Portugal program), and the Maor Foundation. The funding sources did not interfere in any step of the study.

REFERENCES

- Sinn HP, Kreipe H. A brief overview of the WHO classification of breast tumors, 4th edition, focusing on issues and updates from the 3rd edition. *Breast Care (Basel)* 2013;8:149–154.
- Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. *Br J Cancer* 2005;93:1046–1052.
- Li CI, Andreson BO, Daling JR et al. Trends in Incidence Rates of Invasive Lobular and Ductal Breast Carcinoma. *JAMA* 2003;289:1421–1424.
- Li CI, Anderson BO, Porter P et al. Changing incidence rate of invasive lobular breast carcinoma among older women. *Cancer* 2000;88:2561–2569.
- Rakha EA, Ellis IO. Lobular breast carcinoma and its variants. *Semin Diagn Pathol* 2010;27:49–61.
- McCart Reed AE, Kutasovic JR, Lakhani SR et al. Invasive lobular carcinoma of the breast: Morphology, biomarkers and 'omics. *Breast Cancer Res* 2015;17:12.
- Desmedt C, Zoppoli G, Gundem G et al. Genomic characterization of primary invasive lobular breast cancer. *J Clin Oncol* 2016;34:1872–1881.
- Katz A, Saad ED, Porter P et al. Primary systemic chemotherapy of invasive lobular carcinoma of the breast. *Lancet Oncol* 2007;8:55–62.
- Truin W, Voogd AC, Vreugdenhil G et al. Effect of adjuvant chemotherapy in postmenopausal patients with invasive ductal versus lobular breast cancer. *Ann Oncol* 2012;23:2859–2865.
- Metzger Filho O, Giobbie-Hurder A, Mallon E et al. Relative effectiveness of letrozole compared with tamoxifen for patients with lobular carcinoma in the BIG 1-98 trial. *J Clin Oncol* 2015;33:2772–2779.
- Knauer M, Gruber C, Dietze O et al. Survival advantage of anastrozole compared to tamoxifen for lobular breast cancer in the ABCSG-8 study. *Cancer Res* 2015;75(suppl 9):S2-06a.
- Rakha EA, Gill MS, El-Sayed ME et al. The biological and clinical characteristics of breast carcinoma with mixed ductal and lobular morphology. *Breast Cancer Res Treat* 2009;114:243–250.
- Bharat A, Gao F, Margenthaler JA. Tumor characteristics and patient outcomes are similar between invasive lobular and mixed invasive ductal/lobular breast cancers but differ from pure invasive ductal breast cancers. *Am J Surg* 2009;198:516–519.
- Suryadevara A, Paruchuri LP, Banisaeed N et al. The clinical behavior of mixed ductal/lobular carcinoma of the breast: A clinicopathologic analysis. *World J Surg Oncol* 2010;8:51.
- Zengel B, Yarasbas U, Duran A et al. Comparison of the clinicopathological features of invasive ductal, invasive lobular, and mixed (invasive ductal + invasive lobular) carcinoma of the breast. *Breast Cancer* 2015;22:374–381.
- Arps DP, Healy P, Zhao L et al. Invasive ductal carcinoma with lobular features: A comparison study to invasive ductal and invasive lobular carcinomas of the breast. *Breast Cancer Res Treat* 2013;138:719–726.
- Pestalozzi BC, Zahrieh D, Mallon E et al. Distinct clinical and prognostic features of infiltrating lobular carcinoma of the breast: Combined results of 15 international breast cancer study group clinical trials. *J Clin Oncol* 2008;26:3006–3014.
- Wasif N, Maggard MA, Ko CY et al. Invasive lobular vs. ductal breast cancer: A stage-matched comparison of outcomes. *Ann Surg Oncol* 2010;17:1862–1869.
- Cristofanilli M, Gonzalez-Angulo A, Sneige N et al. Invasive lobular carcinoma classic type: Response to primary chemotherapy and survival outcomes. *J Clin Oncol* 2005;23:41–48.
- 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.
- Colleoni M, Rotmensz N, Maisonneuve P et al. Outcome of special types of luminal breast cancer. *Ann Oncol* 2012;23:1428–1436.
- Xiao Y, Ma D, Ruan M et al. Mixed invasive ductal and lobular carcinoma has distinct clinical features and predicts worse prognosis when stratified by estrogen receptor status. *Sci Rep* 2017;7:10380.
- Ciriello G, Gatza ML, Beck AH et al. Comprehensive molecular portraits of invasive lobular breast cancer. *Cell* 2015;163:506–519.
- Talman ML, Jensen MB, Rank F. Invasive lobular breast cancer. Prognostic significance of histological malignancy grading. *Acta Oncol* 2007;46:803–809.
- Rakha EA, El-Sayed ME, Menon S et al. Histologic grading is an independent prognostic factor in invasive lobular carcinoma of the breast. *Breast Cancer Res Treat* 2008;111:121–127.
- Early Breast Cancer Trialists, Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: Patient-level meta-analysis of the randomised trials. *Lancet* 2015;386:1341–1352.
- Dabbs DJ, Bhargava R, Chivukula M. Lobular versus ductal breast neoplasms: The diagnostic utility of P120 catenin. *Am J Surg Pathol* 2007;31:427–437.

AUTHOR CONTRIBUTIONS

Conception/design: Otto Metzger-Filho, Arlindo R. Ferreira
Provision of study material or patients: Otto Metzger-Filho, Arlindo R. Ferreira
Collection and/or assembly of data: Otto Metzger-Filho, Arlindo R. Ferreira
Data analysis and interpretation: Otto Metzger-Filho, Arlindo R. Ferreira, Rinath Jeselsohn, William T. Barry, Deborah A. Dillon, Jane E. Brock, Ines Vaz-Luis, Melissa E. Hughes, Eric P. Winer, Nancy U. Lin
Manuscript writing: Otto Metzger-Filho, Arlindo R. Ferreira, Rinath Jeselsohn, William T. Barry, Deborah A. Dillon, Jane E. Brock, Ines Vaz-Luis, Melissa E. Hughes, Eric P. Winer, Nancy U. Lin
Final approval of manuscript: Otto Metzger-Filho, Arlindo R. Ferreira, Rinath Jeselsohn, William T. Barry, Deborah A. Dillon, Jane E. Brock, Ines Vaz-Luis, Melissa E. Hughes, Eric P. Winer, Nancy U. Lin

DISCLOSURES

William T. Barry: Pfizer (RF); **Deborah A. Dillon:** Oncology Analytics, Inc. (C/A, SAB). **Eric P. Winer:** Genentech, Leap, Glaxo-Smith Kline, Eli Lilly & Co., Infinite MD, Carrick Therapeutics (H), Verastem (OI). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board



See <http://www.TheOncologist.com> for supplemental material available online.