

# A Comparison of the Clinicopathological Features, Metastasis Sites and Survival Outcomes of Invasive Lobular, Invasive Ductal and Mixed Invasive Ductal and Lobular Breast Carcinoma

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## ABSTRACT

**Objective:** We compared the breast cancer patients with invasive lobular carcinoma (ILC), invasive ductal carcinoma (IDC) and mixed invasive ductal and lobular carcinoma (IDLC) in terms of clinicopathological and treatment features, metastatic patterns and long-term survival.

**Materials and Methods:** In a 10 years patient cohort, 3412 patients with unilateral breast carcinoma were enrolled in the study. Tumors were classified histologically according to criteria described by World Health Organization classification.

**Results:** The highest rate of T3 tumors were found in IDLC patients, the lowest in IDC patients, and the difference between groups was significant only in comparison of IDC vs IDLC. Axillary positivity rate was highest in IDLC, lowest in ILC; differences were significant in comparisons of IDLC vs ILC and IDLC vs IDC. There was no significant difference between the patient groups in terms of surgical treatment, mastectomy and breast conserving surgery. Rate of bone metastasis was highest in IDLC, lowest in IDC, with significant difference between IDLC and IDC. Locoregional recurrence-free survival (LRFS) rate was 90.9% in ILC patients, 92.5% in IDC patients, 92.9% in IDLC patients, with no significant difference between the groups; in multivariate Cox analysis, histological type had no prognostic significance ( $p=0.599$ ). Distant metastasis-free survival (DMFS) rate was 66.2% in ILC patients, 66.7% in IDC patients, 57.1% in IDLC patients; in multivariate Cox analysis, histological type had no prognostic significance ( $p=0.392$ ).

**Conclusion:** Although these results suggest that IDLC may have a worse prognosis than IDC and ILC, in multivariate analysis LRFS and DMFS were not significantly different among the histological type groups.

**Keywords:** Breast cancer, Invasive lobular carcinoma, Invasive ductal carcinoma, mixed invasive ductal and lobular carcinoma, survival

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## Introduction

Invasive breast cancer is a histologically heterogeneous disease; among numerous histological types, invasive ductal carcinoma (IDC) is the most common, present in 70%-75% of the cases (1, 2), followed by invasive lobular carcinoma (ILC), present in 5%-15% of the cases (1-3). Mixed invasive ductal and lobular carcinoma (IDLC), which has characteristics of both invasive ductal and lobular carcinoma, is present in approximately 5% of the cases (2). Lately, the prevalence of the lobular breast tumors has been on the rise, particularly in postmenopausal women; this increase has been linked with evidence suggesting that frequent use of hormone replacement therapy in recent years has increased the risk of ILC and IDLC development more than that of IDC (4-6). Clinicopathological characteristics and survival outcomes of ILC and IDC have been compared in numerous studies with conflicting results. On the other hand, few studies have compared IDLC with ILC and IDC.

In this study, we compared ILC, IDC and IDLC in terms of clinicopathological and treatment features, metastatic patterns and long-term survival retrospectively in a 10 years patient cohort.

## Materials and Methods

### Ethical standards

The research protocol of this clinical study was approved by the Ethics Committee of the University of Health Sciences, İstanbul Okmeydanı Training and Research Hospital (the date/protocol number: 04.24.2019/1236). The study was conducted according to the

principles of the Helsinki Declaration and its later amendments or comparable ethical standards. In addition, all patients were routinely informed about the procedures and their written informed consent was obtained.

### Patients

We reviewed the file records of women who underwent surgery for breast carcinoma between January 1993 and December 2002 who were then followed up in Istanbul Okmeydanı Training and Research Hospital. Inclusion criteria for the patients were a histological diagnosis of unilateral breast ILC, IDC and IDLC; tumors were classified histologically according to criteria described by World Health Organization classification; no previous or concomitant malignant disease; known pathological tumor size (patients with T4 tumor were not included), for multifocal/multicentric (MFMC) tumors, largest dimension of the largest tumor was accepted as the tumor size; at least one lymph node removed by axillary dissection; no metastasis in ipsilateral internal mammary or supraclavicular lymph nodes and distant sites at the time of diagnosis; microscopically tumor-free surgical margins; completion of adjuvant therapy planned according to standard therapy protocols (patients received neoadjuvant therapy were not included); and a follow-up period at least five years in patients without disease recurrence. A total of 3412 patients (including 668 patients who underwent surgery at the study hospital) who met these criteria were enrolled in the current study.

Removal of at least six nonmetastatic lymph nodes is required to describe the axillary lymph node status as “negative” according to TNM classification (7). Thus, within the node-negative patient group, 132 patients (nine patients with ILC, 118 patients with IDC, five patients with IDLC) with one to five lymph node(s) removed by axillary dissection were not included in the analyses of axillary status assessment and survival.

Follow-up data were obtained from file records and, in some patients, through telephone calls. The endpoint of the study was first disease recurrence. Locoregional recurrence was defined as the recurrence involving the chest wall or tumor excision site in the breast (local) or/and ipsilateral axillary, supraclavicular and internal mammary lymph nodes (regional). Locoregional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) times were defined as the time interval between tumor excision and detection of first locoregional recurrence or distant metastasis, respectively, or the date of last follow-up. In 147 patients who developed a second malignancy (excluding three patients with basal cell carcinoma), the diagnosis date of second malignancy was considered as the last follow-up date. In 66 patients whose death was unrelated to cancer, the date of death was considered as the last follow-up date.

### Statistical analysis

The chi-squared and Fisher’s exact tests were used to evaluate the differences between proportions and Student’s *t*-test was used to evaluate the continuous data for comparisons of the clinicopathological and treatment features, metastatic pattern and metachronous contralateral breast cancer development of the patient groups. Kaplan-Meier method was used for calculation and plotting of the LRFS and DMFS curves of the patient groups, and log-rank test was used for the comparison of the survival curves. The relative importance of the prognostic features was investigated using the Cox proportional hazards model; prognostic parameters present in all patients were included in the Cox analysis. All comparisons were two-tailed, and *p*

value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Clinicopathological features

Among 3621 patients, including 209 patients with invasive carcinoma of other histological types (mucinous, medullary, papillary, metaplastic and other) who were in the patient cohort during the same period but not included in this study, 272 (7.5%) had ILC, 2981 (82.3%) had IDC, and 159 (4.4%) had IDLC. Clinicopathological features of 3412 patients are shown in Table 1. Patients with ILC had the highest mean age, while patients with IDLC had the lowest; significant age difference was found for comparisons of ILC vs IDC and ILC vs IDLC. Considering age status according to the cutoff of 35 years, there was no significant difference among the histological types in the rates of the patients below 35 years and 35 and above 35 years. The rate of postmenopausal patients was highest in ILC group and lowest in IDLC group; no significant difference was detected in comparison of ILC vs IDC, while the rate of postmenopausal women in IDLC group was significantly lower than those in the ILC and IDC groups. Mean tumor size was largest in IDLC patients, smallest in IDC patients; the difference was borderline significant for comparison of ILC vs IDC ( $p=0.051$ ), significant for IDC vs IDLC, not significant for ILC vs IDLC. According to TNM classification, the highest rate of T1 tumors were found in IDC patients, lowest in IDLC patients; the highest rate of T3 tumors were found in IDLC patients, the lowest in IDC patients, and the difference between groups was significant only in comparison of IDC vs IDLC. The rate of MFMC tumors was highest in IDLC patients, and the difference was statistically significant compared with both ILC and IDC; there was no significant difference between ILC and IDC.

During the examination period of this study patients, vascular invasion, perineural invasion, estrogen receptor (ER) and progesterone receptor (PR) evaluations were not performed routinely in our hospital and in our country. Even though the number of patients having these evaluations was not high, we analyzed the available data. Vascular invasion rate was lowest in ILC, highest in IDC; the difference was significant for comparison of ILC vs IDC, while other group comparisons showed no significant difference. Perineural invasion rate was highest in IDLC, lowest in IDC; the difference was significant in comparison of IDLC vs IDC, while IDLC vs ILC difference was close to the level of significance ( $p=0.076$ ). ER positivity rate was highest in IDLC, lowest in IDC; the difference between groups was significant only in comparison of IDLC vs IDC. PR positivity rate was highest in IDLC, lowest in IDC; this rate was significantly higher in IDLC compared with ILC and IDC. In the evaluation of axillary lymph node status, axillary positivity rate was highest in IDLC, lowest in ILC; differences were significant in comparisons of IDLC vs ILC and IDLC vs IDC, but not significant for ILC vs IDC.

### Treatment features

Surgery and adjuvant treatment features of patients are presented in Table 2. There was no significant difference among histological type groups in terms of surgery, adjuvant hormonal therapy, and radiotherapy. Adjuvant chemotherapy application was highest rate in IDLC patients, lowest rate in ILC patients; the difference was significant in comparison of ILC vs IDC and ILC vs IDLC, but not significant for IDC vs IDLC.

Table 1. Clinicopathological features of the patients

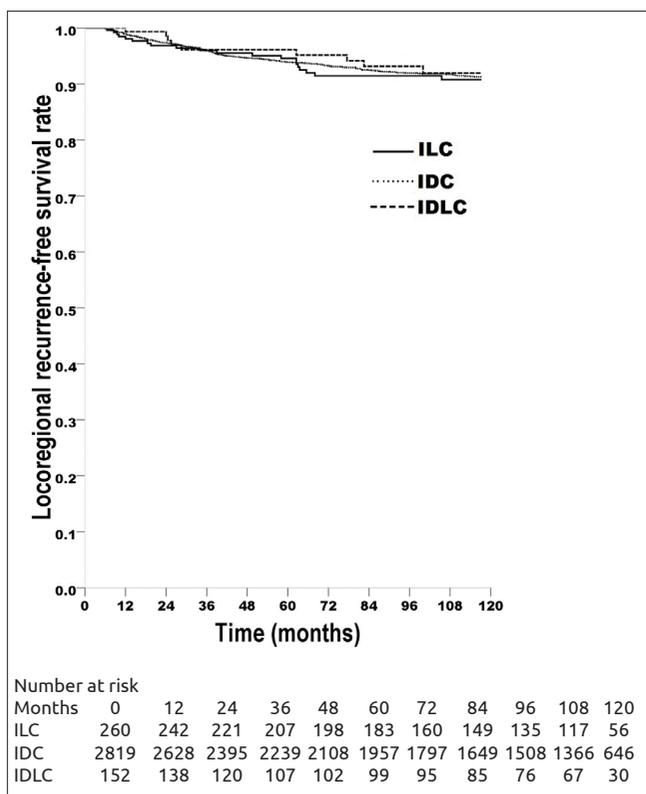
Feature	ILC		IDC		IDLC		p		
	n	%	n	%	n	%	ILC vs IDC	ILC vs IDLC	IDC vs IDLC
Age, years							0.023	0.008	0.119
Mean (SD)	50.9 (11.2)		49.3 (11.0)	47.9 (11.3)					
Median	49.5		48.0		47.0				
Range	24.0-84.0		20.0-86.0	22.0-80.0					
Age, years							0.377	0.305	0.602
<35	17	6.3	237	8.0	15	9.4			
≥35	255	93.7	2744	92.0	144	90.6			
Menopausal status							0.188	0.006	0.021
Premenopausal	129	47.4	1538	51.6	97	61.0			
Postmenopausal	143	52.6	1443	48.4	62	39.0			
Tumor size, cm							0.051	0.132	0.002
Mean (SD)	3.3 (2.0)	3.1 (1.8)	3.6 (2.1)						
Median	3.0	2.9	3.0						
Range	0.3-13.0	0.2-15.0	0.7-11.0						
Tumor size, TNM							0.204	0.367	0.008
T1	86	31.6	966	32.4	42	26.4			
T2	143	52.6	1654	55.5	85	53.5			
T3	43	15.8	361	12.1	32	20.1			
MFMC tumors							0.790	0.001	<0.001
Yes	17	6.3	205	6.9	26	16.4			
No	255	93.7	2776	93.1	133	83.6			
Vascular invasion							0.047	0.521	0.292
Negative	65	52.4	751	43.3	56	48.3			
Positive	59	47.6	985	56.7	60	51.7			
Unknown	148		1245		43				
Perineural invasion							0.371	0.076	0.001
Negative	52	66.7	759	72.1	40	52.6			
Positive	26	33.3	294	27.9	36	47.4			
Unknown	194		1928		83				
Estrogen receptor							0.288	0.149	0.008
Negative	45	34.9	631	39.6	24	25.8			
Positive	84	65.1	961	60.4	69	74.2			
Unknown	143		1389		66				
Progesterone receptor							0.122	0.047	<0.001
Negative	42	33.9	636	41.0	18	20.5			
Positive	82	66.1	917	59.0	70	79.5			
Unknown	148		1428		71				
Axillary lymph node status							0.391	0.029	0.046
Negative	103	39.2	1045	36.5	44	28.6			
Positive	160	60.8	1818	63.5	110	71.4			

ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; IDLC: mixed invasive ductal and lobular carcinoma; SD: standard deviation; MFMC: Multifocal or Multicentric

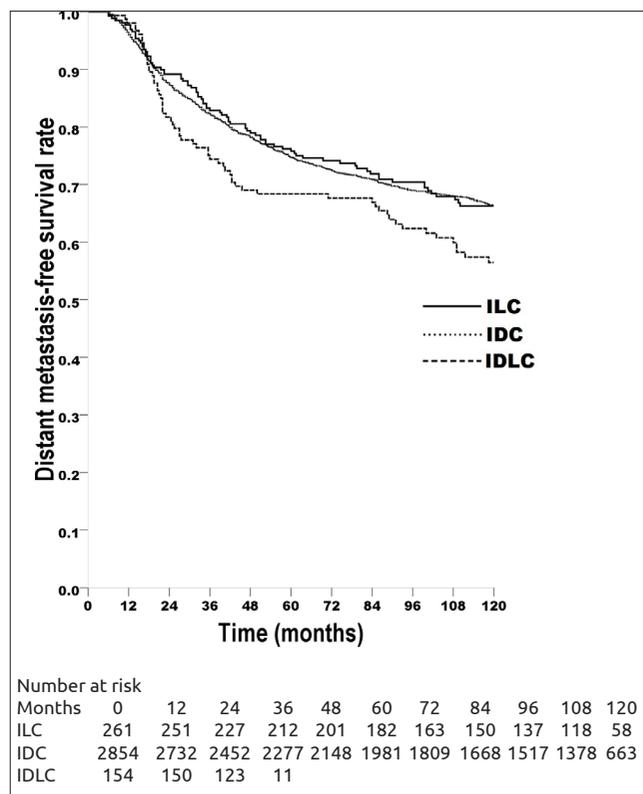
Table 2. Treatment features of the patients

Feature	ILC		IDC		IDLC		p		
	n	%	n	%	n	%	ILC vs IDC	ILC vs IDLC	IDC vs IDLC
Surgery							0.998	0.904	0.829
Mastectomy	244	89.7	2674	89.7	144	90.6			
Breast-conserving	28	10.3	307	10.3	15	9.4			
Chemotherapy							0.009	0.010	0.200
Yes	202	74.3	2409	80.8	135	84.9			
No	70	25.7	572	19.2	24	15.1			
Hormonal therapy							0.161	0.742	0.484
Yes	199	73.2	2059	69.1	114	71.7			
No	73	26.8	922	30.9	45	28.3			
Radiotherapy							0.502	0.086	0.116
Yes	184	67.6	2075	69.6	120	75.5			
No	88	32.4	906	30.4	39	24.5			

ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; IDLC: mixed invasive ductal and lobular carcinoma



**Figure 1.** Locoregional recurrence-free survival (LRFS) rates of the breast carcinoma patients with invasive lobular carcinoma (ILC, 263 patients, LRFS rate 90.9%), with invasive ductal carcinoma (IDC, 2863 patients, LRFS rate 92.5%), with mixed invasive ductal and lobular carcinoma (IDLC, 154 patients, LRFS rate 92.9%). ILC vs IDC, log-rank  $\chi^2=0.842$ ,  $p=0.359$ ; ILC vs IDLC, log-rank  $\chi^2=0.295$ ,  $p=0.587$ ; IDC vs IDLC, log-rank  $\chi^2=0.000$ ,  $p=0.993$ .



**Figure 2.** Distant metastasis-free survival (DMFS) rates of the breast carcinoma patients with invasive lobular carcinoma (ILC, 263 patients, DMFS rate 66.2%), with invasive ductal carcinoma (IDC, 2863 patients, DMFS rate 66.7%), with mixed invasive ductal and lobular carcinoma (IDLC, 154 patients, DMFS rate 57.1%). ILC vs IDC, log-rank  $\chi^2=0.040$ ,  $p=0.842$ ; ILC vs IDLC, log-rank  $\chi^2=3.065$ ,  $p=0.080$ ; IDC vs IDLC, log-rank  $\chi^2=5.867$ ,  $p=0.015$ .

**Metastasis sites and metachronous contralateral breast carcinoma**  
 Table 3 presents data regarding the location of metastases (in one site or more sites concomitantly) and the development of metachronous contralateral breast carcinoma for the whole series encompass-

ing 3412 patients. There was no significant difference among the histological type groups in terms of metastasis to unilateral axillary lymph nodes. Distant metastasis sites were not significantly different among the groups except for the bone. Development rate of

**Table 3. Metastasis sites and metachronous contralateral breast carcinoma in patient groups according to histological types**

Metastasis sites	ILC		IDC		IDLC		p		
	n	%	n	%	n	%	ILC vs IDC	ILC vs IDLC	IDC vs IDLC
Axillary lymph nodes							0.929	0.410	0.325
Yes	4	1.5	52	1.7	5	3.1			
No	268	98.5	2929	98.3	154	96.9			
Bone							0.162	0.085	0.001
Yes	54	19.9	493	16.5	43	27.0			
No	218	80.1	2488	83.5	116	73.0			
Lung							0.429	1.000	0.700
Yes	25	9.2	320	10.7	15	9.4			
No	247	90.8	2661	89.3	144	90.6			
Pleura							0.961	0.591	0.306
Yes	4	1.5	51	1.7	5	3.1			
No	268	98.5	2930	98.3	154	96.9			
Liver							0.779	0.519	0.574
Yes	18	6.6	217	7.3	14	8.8			
No	254	93.4	2764	92.7	145	91.2			
Central nervous system							0.071	1.000	0.235
Yes	3	1.1	98	3.3	2	1.3			
No	269	98.9	2883	96.7	157	98.7			
Gynecologic							1.000	1.000	1.000
Yes	1	0.4	6	0.2	0	0.0			
No	271	99.6	2975	99.8	159	100.0			
Distant lymph nodes							0.146	1.000	0.265
Yes	10	3.7	63	2.1	6	3.8			
No	262	96.3	2918	97.9	153	96.2			
Skin-subcutaneous							0.545	1.000	1.000
Yes	1	0.4	8	0.3	0	0.0			
No	271	99.6	2973	99.7	159	100.0			
Adrenal							1.000	-	1.000
Yes	0	0.0	5	0.2	0	0.0			
No	272	100.0	2976	99.8	159	100.0			
Peritoneum							0.354	1.000	0.229
Yes	1	0.4	4	0.1	1	0.6			
No	271	99.6	2977	99.9	158	99.4			
Contralateral breast carcinoma							0.496	0.252	0.405
Yes	3	1.1	56	1.9	5	3.1			
No	269	98.9	2925	98.1	154	96.9			

ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; IDLC: mixed invasive ductal and lobular carcinoma

bone metastasis was highest in IDLC patients, lowest in IDC patients; the difference was significant in comparison of IDC vs IDLC, but not significant for ILC vs IDC and ILC vs IDLC. In addition to metastasis sites reported in Table 3, metastases developed in cecum, pancreas, urinary bladder, thyroid, pericardium, retroperitoneal soft

tissue in one patient each and in the eye in two patients. Due to their low numbers, these locations were not considered in the statistical analysis. The rates of metachronous contralateral breast carcinoma were not significantly different among the three histological type groups.

Table 4. Cox proportional hazards model analysis of the clinicopathological and treatment features in terms of locoregional recurrence-free survival

Feature	Relative risk	95% CI	P
Age, years			0.009
<35	1.00		
≥35	0.57	0.38-0.87	
Menopausal status			0.103
Premenopausal	1.00		
Postmenopausal	1.26	0.95-1.67	
Tumor size			<0.001
T1	1.00		
T2	1.72	1.27-2.33	
T3	2.18	1.40-3.41	
Multifocality/multicentricity			0.031
Yes	1.00		
No	0.62	0.40-0.96	
Histological type			0.599
ILC	1.00		
IDC	0.80	0.52-1.23	
IDLC	0.80	0.39-1.63	
Axillary lymph node status			0.018
Negative	1.00		
Positive	1.51	1.07-2.12	
Surgery			0.001
Mastectomy	1.00		
Breast-conserving	1.92	1.29-2.85	
Chemotherapy			0.863
Yes	1.00		
No	1.03	0.70-1.52	
Hormonal therapy			<0.001
Yes	1.00		
No	1.82	1.39-2.38	
Radiotherapy			0.001
Yes	1.00		
No	1.87	1.31-2.66	

CI: confidence interval; ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; IDLC: mixed invasive ductal and lobular carcinoma

### Survival

Survival analyses were conducted on 3280 patients, excluding 132 node-negative patients who had 1-5 lymph node(s) removed by axillary dissection. Until the end of the study on November 2017, 251 patients developed locoregional recurrence, 1107 patients developed distant metastasis, and 57 patients developed concomitant locoregional recurrence and distant metastasis. In patients without disease recurrence, the median follow-up time was 148 months (range:60-297 months).

LRFS rate was 90.9% in ILC patients, 92.5% in IDC patients, 92.9% in IDLC patients, with no significant difference between the groups

(Figure 1); in multivariate Cox analysis, histological type had no prognostic significance ( $p=0.599$ ) (Table 4). DMFS rate was 66.2% in ILC patients, 66.7% in IDC patients, 57.1% in IDLC patients, with no significant difference between the ILC patients and IDC patients (log-rank  $\chi^2=0.040$ ,  $p=0.842$ ); DMFS of IDLC patients was significantly worse than IDC patients (log-rank  $\chi^2=5.867$ ,  $p=0.015$ ); it was also worse than that of ILC patients, but the difference was outside the limit of significance (log-rank  $\chi^2=3.065$ ,  $p=0.080$ ) (Figure 2); in multivariate Cox analysis, histological type had no prognostic significance ( $p=0.392$ ) (Table 5).

Table 5. Cox proportional hazards model analysis of the clinicopathological and treatment features in terms of distant metastasis-free survival

Feature	Relative risk	95% CI	p
Age, years			<0.001
<35	1.00		
≥35	0.68	0.56-0.84	
Menopausal status			0.263
Premenopausal	1.00		
Postmenopausal	1.08	0.94-1.23	
Tumor size			<0.001
T1	1.00		
T2	1.55	1.33-1.82	
T3	2.49	2.05-3.03	
Multifocality/multicentricity			0.001
Yes	1.00		
No	0.72	0.59-0.88	
Histological type			0.392
ILC	1.00		
IDC	0.96	0.77-1.19	
IDLC	1.14	0.83-1.57	
Axillary lymph node status			<0.001
Negative	1.00		
Positive	2.41	1.99-2.93	
Surgery			0.661
Mastectomy	1.00		
Breast-conserving	0.95	0.76-1.19	
Chemotherapy			0.301
Yes	1.00		
No	0.89	0.71-1.11	
Hormonal therapy			<0.001
Yes	1.00		
No	1.36	1.20-1.55	
Radiotherapy			0.068
Yes	1.00		
No	0.83	0.67-1.01	

CI: confidence interval; ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; IDLC: mixed invasive ductal and lobular carcinoma

## Discussion and Conclusion

In our study, comparison of clinicopathological features of patients with ILC, IDC and IDLC revealed highest mean age in ILC, lowest mean age in IDLC, with significant difference in comparisons of ILC vs IDC and ILC vs IDLC. When patients were analyzed in two groups according to 35-year cutoff, no significant difference was found among the histological types. In some studies, significantly advanced age was found in ILC compared with IDC (8-13). In other studies, no significant age difference was found between ILC and

IDC (14-18). In one study, the rate of patients below the age of 50 years was significantly lower in IDLC compared with ILC, while no significant difference was seen between IDLC and IDC (19). In a study comparing IDLC with ILC and IDC, the rate of women over the age of 50 years was significantly higher in ILC (20). In our series, the rate of postmenopausal women was highest in ILC, lowest in IDLC, with significant difference for IDLC vs ILC and IDLC vs IDC comparisons. In a study, menopausal status was not significantly different between ILC and IDC (1). In a study, the rate of postmenopausal patients was significantly lower in IDLC than in

ILC, while no significant difference was found between IDLC and IDC (19). In a study comparing ILC, IDC and IDLC, there was no significant difference between the histological groups in terms of menopausal status (20).

In our study, both mean tumor size and the rate of T3 tumors were highest in IDLC, lowest in IDC, with significant difference between IDLC and IDC. In some studies comparing ILC and IDC, no significant difference was found between the two histological types in terms of tumor size (9, 14, 15, 17, 18, 21, 22); in other studies, tumor size was significantly larger in ILC compared with IDC (1, 8, 10-13, 23); in one study the rate of T1 tumors was significantly lower in ILC compared with IDC (16). In a study comparing IDLC with IDC and ILC, the rate of T3 tumors was significantly higher in IDLC than in IDC, while no significant difference was found between IDLC and ILC (24); in another study, mean tumor size was largest in IDLC, smallest in IDC, with significant difference in histological group comparisons (there were no pairwise comparisons) (20); in another study no significant difference was found in IDLC compared with ILC and IDC in terms of tumor size (19). In our series, the rate of MFMC tumors was highest in IDLC, lowest in ILC, with significant difference found in comparisons of IDLC vs ILC and IDLC vs IDC and no significant difference found for ILC vs IDC. In some studies comparing ILC and IDC, the rate of MFMC tumors was found to be significantly higher in ILC compared with IDC (12, 13, 17, 18). In one study, no significant difference was found between the two histological types in terms of MFMC tumor rate (15). In a study investigating IDLC, ILC and IDC, MFMC tumor rate was found to be significantly higher in ILC (20).

In our series, within the subset of patients with vascular invasion, perineural invasion, ER and PR status evaluations, vascular invasion positivity rate was highest in IDC, lowest in ILC, with significant difference in comparison of ILC vs IDC. In studies comparing ILC and IDC, vascular invasion was significantly lower in ILC vs IDC (1, 9, 23). In our series, the rates of perineural invasion and ER positivity were highest in IDLC, lowest in IDC, with significant difference between IDLC and IDC for both. Similarly, PR positivity rate was highest in IDLC, lowest in IDC, with significant difference detected in comparisons of IDLC vs ILC and IDLC vs IDC. In some studies comparing ILC and IDC, ER and PR positivity were found at significantly higher rates in ILC than in IDC (8, 10-13, 16, 18, 21-23) while some studies found no significant difference between these two histological types in terms of ER status (9,15). In one of the studies comparing IDLC with IDC and ILC, ER positivity rate was significantly higher in IDLC than in IDC, with no significant difference between IDLC and ILC, and PR positivity rate was significantly higher in IDLC than in IDC and ILC (24); in another study, no difference was found between the three histological types in terms of ER and PR positivity (20); in a different study, ER and PR positivity was significantly higher in IDLC and ILC compared with IDC (25).

In our series, the rate of axillary lymph node positivity was highest in IDLC, lowest in ILC, with pairwise comparisons of IDLC vs ILC and IDLC vs IDC significant, while ILC vs IDC was not significant. In some studies comparing ILC and IDC, axillary lymph node positivity rate was not significantly different between ILC and IDC (1, 8-10, 15, 16, 18, 21-23). In other studies, it was significantly lower in ILC compared with IDC (14, 17); in some other studies it was significantly higher in ILC compared with IDC (11, 13). In one study comparing IDLC with IDC and ILC, axillary lymph node positivity

rate was significantly higher in IDLC than in IDC, with no significant difference between IDLC and ILC (24); in another study, there was no significant difference between the three histological types in terms of axillary lymph node positivity (20).

In our study, there was no significant difference between the patient groups according to histological type in terms of surgical treatment, mastectomy and breast-conserving surgery. Among studies comparing ILC and IDC, some had no difference in mastectomy and breast-conserving surgery rates (15, 16, 18, 22); while some found significantly more mastectomy performed in patients with ILC than breast-conserving surgery (1, 8, 10-12), more frequent application of mastectomy in ILC patients may be related to more frequent presence or higher likelihood of multicentric tumors in this histological type. In a study comparing IDLC with IDC and ILC, surgical treatment was not significantly different between the histological groups (20).

In our study, rates of metastasis to various locations did not vary significantly between the histological types, except for bone metastasis. Rate of bone metastasis was highest in IDLC, lowest in IDC, with significant difference between IDLC and IDC. In a study comparing these three histological types, no significant difference was found regarding the metastatic sites (20). Among studies comparing metastatic sites of ILC and IDC, some found no difference between the two histological types (16, 18, 21), while some found significantly higher rates of bone metastasis in ILC (1, 12); some studies found significantly more frequent lung metastases in IDC (1, 10, 12, 22, 26), while one study found it to be significantly higher in ILC (27). Some studies reported the rare occurrence of peritoneum-retroperitoneum metastases, as also seen in our series, and more frequently in ILC than in IDC (26, 27).

In this series, there was no significant difference between the three histological type groups in terms of metachronous contralateral breast cancer occurrence. Some studies found higher rates of metachronous contralateral breast cancer in ILC compared with IDC (10, 14, 16, 28), while others found no significant difference between the two histological types (1, 17, 21, 29, 30).

In our study, LRFS was not statistically significant among the patient groups with three histological types in univariate and multivariate analyses. In univariate analysis, DMFS rate was highest in IDC, lowest in IDLC, with the difference close to the level of significance for IDLC vs ILC and significant for IDLC vs IDC; however, there was no significant difference among the histological groups in multivariate analysis. In various studies comparing survival in ILC and IDC, no significant survival difference was found between the two groups (9, 10, 12, 14-18, 21-23, 26, 31, 32); in some studies, survival was found to be significantly better in ILC compared with IDC (8, 11). In two studies comparing IDLC with ILC and IDC, survival was not significantly different between the groups (19, 20); in another study, IDLC had significantly worse survival compared with IDC, while no significant survival difference was found between IDLC and ILC (24).

In our study two important prognostic factors according to TNM classification, namely tumor size and axillary lymph node status, were not significantly different between ILC and IDC, while IDLC had significantly larger tumor size and higher rates of axillary lymph node positivity than IDC; compared with ILC, IDLC had significantly

higher lymph node positivity rate, but no significant difference in terms of tumor size. Although these results suggest that IDLC may have a worse prognosis than IDC and ILC, in multivariate analysis LRFS and DMFS were not significantly different among the histological type groups. In our series, rates of metastasis to various locations did not vary significantly between the histological types, except for bone metastasis. Rate of bone metastasis was highest in IDLC, lowest in IDC, with significant difference between IDLC and IDC. Since the risk of developing metachronous contralateral breast carcinoma was similar in all three histological type groups, it is reasonable to use a similar approach for all histological types in the evaluation of contralateral breast in post-treatment follow-up of these patients. Retrospective nature of our study is a limitation. Future evaluations of prognostic characteristics of histological types should involve prospective controlled studies and include current, new prognostic characteristics in addition to the clinicopathological characteristics that were available within the period of the present study.

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**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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## References

- Pestalozzi BC, Zahrieh D, Mallon E, Gusterson BA, Price KN, Gelber RD, Holmberg SB, Lindtner J, Snyder R, Thürlimann B, Murray E, Viale G, Castiglione-Gertsch M, Coates AS, Goldhirsch A. 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. (PMID: 18458044) [CrossRef]
- Corben AD. Pathology of invasive breast disease. *Surg Clin North Am* 2013; 93: 363-392. (PMID: 23464691) [CrossRef]
- Mamtani A, King TA. Lobular breast cancer: different disease, different algorithms? *Surg Oncol Clin N Am* 2018; 27: 81-94. (PMID: 29132567) [CrossRef]
- Chen C-L, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. *JAMA* 2002; 287: 734-741. (PMID: 11851540) [CrossRef]
- Li CI, Anderson BO, Daling JR, Moe RE. Trends in incidence rates of invasive lobular and ductal breast carcinoma. *JAMA* 2003; 289: 1421-1424. (PMID: 12636465) [CrossRef]
- Biglia N, Mariani L, Sgro L, Mininanni P, Moggio G, Sismondi P. Increased incidence of lobular breast cancer in women treated with hormone replacement therapy: implications for diagnosis, surgical and medical treatment. *Endocr Relat Cancer* 2007; 14: 549-567. (PMID: 17914088) [CrossRef]
- Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. *AJCC Cancer Staging Handbook*, 7th edn. New York: Springer-Verlag, 2010.
- Silverstein MJ, Lewinsky BS, Waisman JR, Gierson ED, Colburn WJ, Senofsky GM, Gamagami P. Infiltrating lobular carcinoma: is it different from infiltrating duct carcinoma? *Cancer* 1994; 73: 1673-1677. (PMID: 8156495)
- Mersin H, Yıldırım E, Gülben K, Berberoğlu U. Is invasive lobular carcinoma different from invasive ductal carcinoma? *Eur J Surg Oncol* 2003; 29: 390-395. (PMID: 12711296) [CrossRef]
- 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. (PMID: 15084238) [CrossRef]
- 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. (PMID: 20162457) [CrossRef]
- Kwaast AB, Groothuis-Oudshoorn KC, Grandjean I, Ho VK, Voogd AC, Menke-Pluymers MB, van der Sangen MJ, Tjan-Heijnen VC, Kiemeny LA, Siesling S. Histological type is not an independent prognostic factor for the risk pattern of breast cancer recurrences. *Breast Cancer Res Treat* 2012; 135: 271-280. (PMID: 22810087) [CrossRef]
- Brouckaert O, Laenen A, Smeets A, Christiaens MR, Vergote I, Wildiers H, Moerman P, Floris G, Neven P. Prognostic implications of lobular breast cancer histology: new insights from a single hospital cross-sectional study and SEER data. *Breast* 2014; 23: 371-377. (PMID: 24530094) [CrossRef]
- Toikkanen S, Pylkkänen L, Joensuu H. Invasive lobular carcinoma of the breast has better short- and long-term survival than invasive ductal carcinoma. *Br J Cancer* 1997; 76: 1234-1240. (PMID: 9365176) [CrossRef]
- Jayasinghe UW, Bilous AM, Boyages J. Is survival from infiltrating lobular carcinoma of the breast different from that of infiltrating ductal carcinoma? *Breast J* 2007; 13: 479-485. (PMID: 17760669) [CrossRef]
- Cao AY, Huang L, Wu J, Lu JS, Liu GY, Shen ZZ, Shao ZM, Di GH. Tumor characteristics and the clinical outcome of invasive lobular carcinoma compared to infiltrating ductal carcinoma in a Chinese population. *World J Surg Oncol* 2012; 10: 152. (PMID: 22805492) [CrossRef]
- Fortunato L, Mascaro A, Poccia I, Andrich R, Amini M, Costarelli L, Cortese G, Farina M, Vitelli C. Lobular breast cancer: same survival and local control compared with ductal cancer, but should both be treated the same way? Analysis of an institutional database over a 10-year period. *Ann Surg Oncol* 2012; 19: 1107-1114. (PMID: 21913022) [CrossRef]
- Biglia N, Maggiorotto F, Liberale V, Bounous VE, Sgro LG, Pecchio S, D'Alonzo M, Ponzzone R. Clinical-pathologic features, long term-outcome and surgical treatment in a large series of patients with invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC). *Eur J Surg Oncol* 2013; 39: 455-460. (PMID: 23490334) [CrossRef]
- Rakha EA, Gill MS, El-Sayed ME, Khan MM, Hodi Z, Blamey RW, Evans AJ, Lee AH, Ellis IO. The biological and clinical characteristics of breast carcinoma with mixed ductal and lobular morphology. *Breast Cancer Res Treat* 2009; 114: 243-250. (PMID: 18404368) [CrossRef]
- Zengel B, Yazarbas U, Duran A, Uslu A, Elyatkın N, Demirkıran MA, Cengiz F, Şimşek C, Postacı H, Vardar E, Durusoy R. 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. (PMID: 23925582). [CrossRef]
- Korhonen T, Huhtala H, Holli K. A comparison of the biological and clinical features of invasive lobular and ductal carcinomas of the breast. *Breast Cancer Res Treat* 2004; 85: 23-29. (PMID: 15039595). [CrossRef]
- Korhonen T, Kuukasjärvi T, Huhtala H, Alarmo E-L, Holli K, Kallioniemi A, Pylkkänen L. The impact of lobular and ductal breast cancer histology on the metastatic behavior and long term survival of breast cancer patients. *Breast* 2013; 22: 1119-1124. (PMID: 23863867). [CrossRef]
- Molland JG, Donnellan M, Janu NC, Carmalt HL, Kennedy CW, Gillet DJ. Infiltrating lobular carcinoma – a comparison of diagnosis, management and outcome with infiltrating duct carcinoma. *Breast* 2004; 13: 389-396. (PMID: 15454194). [CrossRef]

24. Arps DP, Healy P, Zhao L, Kleer CG, Pang JC. 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. (PMID: 23535842). [[CrossRef](#)]
25. 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. (PMID: 19800459). [[CrossRef](#)]
26. Inoue M, Nakagomi H, Nakada H, Furuya K, Ikegame K, Watanabe H, Omata M, Oyama T. Specific sites of metastases in invasive lobular carcinoma: a retrospective cohort study of metastatic breast cancer. *Breast Cancer* 2017; 24: 667-672. doi: 10.1007/s12282-017-0753-4. (PMID: 28108967). [[CrossRef](#)]
27. Borst MJ, Ingold JA. Metastatic patterns of invasive lobular versus invasive ductal carcinoma of the breast. *Surgery* 1993; 114: 637-642. (PMID: 8211676).
28. Moran MS, Yang Q, Haffty BG. The Yale University experience of early-stage invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC) treated with breast conservation treatment (BCT): analysis of clinical-pathologic features, long-term outcomes, and molecular expression of COX-2, Bcl-2, and p53 as a function of histology. *Breast J* 2009; 15: 571-578. (PMID: 19995377). [[CrossRef](#)]
29. Chung MA, Cole B, Wanebo HJ, Bland KI, Chang HR. Optimal surgical treatment of invasive lobular carcinoma of the breast. *Ann Surg Oncol* 1997; 4: 545-550. (PMID: 9367019). [[CrossRef](#)]
30. Santiago RJ, Harris EER, Qin L, Hwang W-T, Solin LJ. Similar long-term results of breast-conservation treatment for stage I and II invasive lobular carcinoma compared with invasive ductal carcinoma of the breast: the University of Pennsylvania experience. *Cancer* 2005; 103: 2447-2454. (PMID: 15887223). [[CrossRef](#)]
31. Mhuircheartaigh JN, Curran C, Hennessy E, Kerin MJ. Prospective matched-pair comparison of outcome after treatment for lobular and ductal breast carcinoma. *Br J Surg* 2008; 95: 827-833. (PMID: 18498127). [[CrossRef](#)]
32. Viale G, Rotmensz N, Maisonneuve P, Orvieto E, Maiorano E, Galimberti V, Luini A, Colleoni M, Goldhirsch A, Coates AS. Lack of prognostic significance of "classic" lobular breast carcinoma: a matched, single institution series. *Breast Cancer Res Treat* 2009; 117: 211-214. (PMID: 18629634). [[CrossRef](#)]