Invasive lobular carcinoma of the breast: clinicopathological features and patient outcomes

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AIM: *The incidence of invasive lobular carcinoma (ILC), a breast cancer type comprising several variants with distinct morphological and molecular features and clinical behaviors, has been increasing in recent years. Unlike the well-defined classical lobular carcinoma, the most common ILC variant, some uncertainties remain regarding the features of other ILC variants. Therefore, we investigated the clinicopathological features and survival outcomes of specific ILC variants.*
MATERIAL AND METHODS: *This retrospective study compared the tumor and patient characteristics and outcomes according to specific ILC variants in 77 patients who underwent surgery for ILC between January 2010 and December 2016 at a single center in Turkey.*
RESULTS: *The mean patient age was 54.58 ± 11.7 years. The ILC variants were classical, pleomorphic, tubulolobular, solid, and signet ring cell in 49(63.6%), 14(18.2%), 10(12.8%), 2(2.7%), and 2(2.7%) patients, respectively. The mean tumor diameter, histological grade, Ki-67 proliferation index, nodal metastasis, E-cadherin expression, lymphovascular invasion, and type of surgery were significantly different among the variants. However, there were no significant differences in the rates of local recurrence, distant metastasis, and overall survival among the variants.*
CONCLUSIONS: *Despite the good prognostic characteristics and good response to treatment, several studies have reported that ILC is associated with poor long-term outcomes. Therefore, significant challenges remain in the management of ILC. Although it is believed to be a specific histological type, ILC is clinically and pathologically heterogenous. Therefore, the identification of patients with poor prognostic variants should aid in the implementation of efficient and personalized treatment options.*

KEY WORDS: Breast cancer, Invasive cancer, Invasive lobuler carcinoma, Prognosis, Variants of lobuler carcinoma

Introduction

Breast cancer is the most common cancer type, accounting for 23% of all cancers; it is the second most common cause of cancer-related deaths in females [1,2]. The morphology and clinical behavior of the specific variants of invasive lobular carcinoma (ILC), the second most common breast cancer type, are distinct from those of invasive carcinoma-nonspecific type (IC-NST). Low-grade and estrogen receptor-positive ILC typically exhibits good prognosis; however, the rate of metastasis may sometimes be high in patients with ILC [3]. Several studies have demonstrated that long-term outcomes of patients with ILC may be similar or worse than those patients with IC-NST [4,5], illustrating that breast cancer is a heterogeneous disease with different clinical, histological, and biological features and that the treatment varies according to the patient characteristics and cancer subtype [6].

Although several ILC variants have been reported in recent years, their prognostic significance has not yet been fully elucidated [7]. In the 4th edition of the World

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Health Organization breast tumors classification, lobular carcinomas are defined as classic, solid, tubulolobular, alveolar, and pleomorphic variants [8]. In the current study, we aimed to investigate the relationship of the pathological and clinical features of ILC variants with prognosis.

Material and Methods

This retrospective study included the analyses of patient and tumor characteristics according to the ILC variants in 77 patients who underwent surgery for breast cancer and were diagnosed with ILC between January 2010 and December 2016 at our clinic. The inclusion criteria were as follows: (i) histologically confirmed ILC of the breast; (ii) age > 18 years; (iii) written informed consent, with ability to comply with treatment and follow up. Patients with carcinoma *in situ* and bilateral breast cancer, those with a history of neoadjuvant therapy and/or noncurative resection, and those without follow-up for various reasons were excluded from the study. Ethics approval for the study was obtained from the institutional ethics committee and approved by number of 2017/1832.
The preoperative histopathological diagnoses based on the Tru-Cut needle biopsy specimens were postoperatively confirmed. The American Cancer Committee TNM classification was used for tumor staging [9]. The ILC specimens included in the study were re-evaluated for the ILC variants by an experienced breast pathologist. Details

Table I - *Demographics and clinicopathological features of the patients*

Age (year) Mean±SD (Min-Max)		54,6±11,7 (32-81)
Age (year) n (%)	≤50	33 (42,9)
	>50	44 (57,1)
Variants of ILC n (%)	Classical	49 (63,6)
	Pleomorphic	14 (18,2)
	Tubulolobular	10 (13,0)
	Solid	2 (2,6)
	Signet ring	2 (2,6)
Tumor diameter Mean±SD (Min-Max)		2,79±1,48 (1-10)
Stage n (%)	1	26 (33,8)
	2	33 (42,9)
	3	14 (18,2)
	4	4 (5,2)
Multicentricity n (%)	No	57 (74)
	Yes	20 (26)
Histological grade n (%)	1	31 (40,3)
	2	41 (53,2)
	3	5 (6,5)
ER n (%)	Negative	9 (11,7)
	Positive	68 (88,3)
PR n (%)	Negative	8 (10,4)
	Positive	69 (89,6)
C-ERB n (%)	Negative	62 (80,5)
	Positive	15 (19,5)
Ki 67 Mean±SD (Min-Max)		14,1±12,7 (1-60)
Ki 67 n (%)	<14	48 (62,3)
	≥14	29 (37,7)
Number of lymph nodes Mean±SD (Min-Max)		2,0±3,9 (0-22)
Number of metastatic lymph nodes n (%)	Negative	34 (44,2)
	1-3	31 (40,3)
	>3	12 (15,6)
E-Cadherin n (%)	Negative	15 (19,5)
	Positive	13 (16,9)
	None	49 (63,6)
Lymphovascular invasion n (%)	No	36 (46,8)
	Yes	41 (53,2)
Type of surgical procedure n (%)	BCS	26 (33,8)
	Diğer	51 (66,2)
Local recurrence n (%)	No	71 (92,2)
	Yes	6 (7,8)
Distant metastasis n (%)	No	73 (94,8)
	Yes	4 (5,2)
Status of patients n (%)	Alive	71 (92,2)
	Exitus	6 (7,8)

ILC: Invasive lobular carcinoma, ER: Estrogen receptor, PR: Progestron receptor, BCS: Breast conserving surgery

TABLE II - Clinicopathological features among different variants of ILC

		Variants of ILC					
		Classical	Pleomorphic	Tubulolobular	Solid	Signet ring	
Age (year) Mean±SD		54,6±11,9	54,5±12,2	52,7±12,1	58,5±13,4	60,0±4,2	0,845
Age (year) n (%)	≤50	20 (40,8)	7 (50,0)	5 (50,0)	1 (50,0)	0 (0,0)	0,785
	>50	29 (59,2)	7 (50,0)	5 (50,0)	1 (50,0)	2 (100)	
Tumor diameter Mean±SD		2,56±1,10	3,96±2,31	1,77±0,31	4,25±0,35	3,85±1,20	0,002
Stage n (%)	1	21 (42,9)	2 (14,3)	3 (30,0)	0 (0,0)	0 (0,0)	0,209
	2	19 (38,8)	5 (35,7)	6 (60,0)	2 (100)	1 (50,0)	
	3	7 (14,3)	5 (35,7)	1 (10,0)	0 (0,0)	1 (50,0)	
	4	2 (4,1)	2 (14,3)	0 (0,0)	0 (0,0)	0 (0,0)	
Multicentricity n (%)		10 (21,3)	6 (42,9)	2 (20,0)	1 (50,0)	1 (50,0)	0,315
Histological grade n (%)	1	19 (38,8)	2 (14,3)	9 (90,0)	1 (50,0)	0 (0,0)	0,003
	2	26 (53,1)	12 (85,7)	1 (10,0)	1 (50,0)	1 (50,0)	
	3	4 (8,2)	0 (0,0)	0 (0,0)	0 (0,0)	1 (50,0)	
ER n (%)		44 (89,8)	11 (78,6)	9 (90,0)	2 (100)	2 (100)	0,703
PR n (%)		45 (91,8)	11 (78,6)	9 (90,0)	2 (100)	2 (100)	0,571
C-ERB n (%)		12 (24,5)	2 (14,3)	0 (0,0)	0 (0,0)	1 (50,0)	0,247
Ki 67 Mean±SD		13,7±12,9	17,8±7,9	6,2±3,9	20,0±14,1	32,5±38,9	0,005
Ki6 7 n (%)	<14	32 (65,3)	5 (35,7)	9 (90,0)	1 (50,0)	1 (50,0)	0,049
	≥14	17 (34,7)	9 (64,3)	1 (10,0)	1 (50,0)	1 (50,0)	
Number of lymph nodes Mean±SD (Min-Max)		1,27±2,44	5,71±6,97	0,90±0,88	0,00±0,00	2,50±2,12	0,031
Number of metastatic lymph nodes n (%)	Negative	25 (51,0)	4 (28,6)	3 (30,0)	2 (100)	0 (0,0)	0,002
	1-3	20 (40,8)	3 (21,4)	7 (70,0)	0 (0,0)	1 (50,0)	
	>3	4 (8,2)	7 (50,0)	0 (0,0)	0 (0,0)	1 (50,0)	
E-Caderin n (%)	Negative	8 (16,3)	5 (35,7)	2 (20,0)	0 (0,0)	0 (0,0)	0,027
	Positive	4 (8,2)	3 (21,4)	4 (40,0)	1 (50,0)	1 (50,0)	
	None	37 (75,5)	6 (42,9)	4 (40,0)	1 (50,0)	1 (50,0)	
Lymphovascular invasion n (%)		29 (59,2)	8 (57,1)	2 (20,0)	0 (0,0)	2 (100)	0,042
BCS n (%)		18 (36,7)	0 (0,0)	8 (80,0)	0 (0,0)	0 (0,0)	<0,001
Local recurrence n (%)		4 (8,2)	1 (7,1)	0 (0,0)	0 (0,0)	1 (50,0)	0,346
Distant metastasis n (%)		2 (4,1)	2 (14,3)	0 (0,0)	0 (0,0)	0 (0,0)	0,392
Status of patients (exitus) n (%)		3 (6,1)	3 (21,4)	0 (0,0)	0 (0,0)	0 (0,0)	0,373

ILC: Invasive lobular carcinoma, ER: Estrogen receptor, PR: Progestron receptor, BCS: Breast conserving surgery

of tumor size, histological grade, lymphovascular invasion, lymph node metastasis, tumor stage, hormone receptor status [estrogen receptor (ER), progesterone receptor (PR), and HER2], treatments, local and/or distant metastasis, and patient prognosis were reviewed. The ER and PR status was considered positive in specimens in which at least 1% of the tumor cells exhibited nuclear positivity. HER2 positivity was defined as a score of 3+ by silver *in situ* hybridization or HER2 gene amplification determined by immunochemistry. The Ki-67 proliferation index cutoff value was set at 14%.

The surgical procedures performed in the study cohort were mastectomy (modified radical mastectomy, simple mastectomy, or subcutaneous mastectomy) and lumpectomy with sentinel lymph node biopsy. Postoperative radiotherapy was performed in patients with a tumor diameter of >5 cm, those with the involvement of four or more axillary lymph nodes (ALNs), and those who underwent lumpectomy. Postoperative chemotherapy, hormone therapy, or both were performed according to the tumor characteristics of each patient. Local recurrence, distant metastasis, and overall survival rates were also reviewed.

The results were analyzed using SPSS version 15.0 (Statistical Package for the Social Sciences Inc, Chicago, USA). Numerical variables were expressed as means ± standard deviation or with minimum and maximum values, whereas categorical variables were presented as absolute values with percentages. The Kruskal-Wallis test was used for multiple comparisons, and Mann-Whitney U test was used for comparing continuous variables. The Bonferroni method was used to adjust individual p values to determine overall significance levels depending on the number of the tested parameters (p adjusted= individual p value × number of parameters tested). Clinically relevant differences were defined using the chi-squared test or the Monte Carlo simulation, as appropriate.

A p value of <0.05 was considered to indicate statistical significance.

Results

In the current study cohort of 77 patients who underwent surgery for breast cancer and were diagnosed with ILC, the mean age was 54.58 ± 11.7 (range, 32-81) years. Mastectomy and breast-conserving surgery were performed in 66.2% and 33.8% patients, respectively. The ILC variants in the current study were classical, pleomorphic, tubulolobular, solid, and signet ring cell in 63.6% (n = 49), 18.2% (n = 14), 13% (n = 10), 2.6% (n = 2), and 2.6% (n = 2) of the patients, respectively. The MKC ratio (80%) was significantly higher in the tubulolobular variant of ILC than in the other variants ($p < 0.001$). The mean tumor diameter was 2.79 ± 1.48 (range, 1-10) cm, and the multicentricity rate was 26% (n = 20). The mean tumor diameter was significantly larger in the solid and signet ring cell variants than in the other variants ($p = 0.002$). Lymphovascular invasion, which was found in 53.2% (n = 41) of the patients, was a significant poor prognostic factor in the signet ring cell variant of ILC ($p = 0.042$). The mean number of metastatic lymph nodes was 2.0 ± 3.9 (range, 0−22), and 55.8% of the patients had ALN metastases. The rate of ALN metastasis was significantly higher in the pleomorphic and signet ring cell variants than in the other variants of ILC ($p = 0.002$) (Tables I, II).

The cohort patients were also categorized according to their receptor status. Accordingly, 88.3%, 89.6%, and 80.5% of the patients were ER-positive, PR-positive, and HER2-negative, respectively. The receptor status was not significantly different among the ILC variants. The mean Ki-67 proliferation index of the entire cohort was 14.1% ± 12.7% (1%−60%), and the mean Ki-67 proliferation index >14% in the pleomorphic, solid, and signet ring cell variants of ILC ($p = 0.005$) (Table 2).

The classification of patients according to the histological grade revealed that most of the patients with the tubulolobular variant were grade 1 (90.0%, n = 9) and that most of the patients with the pleomorphic variant were grade 2 (85.7%, n = 12).

The rates of local recurrence, distant metastasis, and overall survival were 7.8%, 5.2%, and 92.2%, respectively. There were no significant differences in the rates of local recurrence, distant metastasis, and overall survival among the different variants of the ILC.

Discussion

Invasive breast cancer is currently classified into specific subtypes, including lobular, tubular, papillary, and mucinous as the most common ones, and IC-NST; the specific subtypes and IC-NST constitute approximately 20%−25% and 60%−75% of all breast cancers, respectively [10,11]. Among the specific subtypes, ILC comprises approximately 5%−15% of all breast carcinomas and is the second most common breast malignancy [12]. ILC is histopathologically different from non-specific ductal carcinoma; more importantly, ILC exhibits specific behavioral patterns [13]. The complex structure of ILC can be partially attributable to its numerous variants, including the solid, alveolar, pleomorphic, mixed ductal/lobular, tubulolobular, signet ring cell, and histiocytic variants [13,14]. Except for the pleomorphic variant, information on the biological structure, clinical behavior, and effective treatment strategies for the ILC variants are limited [15,16]. Only a small number of molecular studies have demonstrated that the behavior of alveolar and solid types is similar to that of the classical type [17]. The classic variant is the most common ILC variant, with LN positivity observed in up to 90% of the cases [18]. The mean patient age in the current study coincided with the postmenopausal period, and there were no differences in age among the variants. Of the total 77 cases, 28 were non-classical variants, and pleomorphic ILC was the most common variant (18.2%). The World Health Organization did not consider pleomorphic ILC as a lobular cancer until 2003 [19]. Owing to its high histologic grade, poor ER positivity, strong HER2 status, and the associated poor prognosis, this variant has been considered as a separate breast cancer type. However, Norenda et al. [20] reported that compared with classical ILC, pleomorphic ILC is not an aggressive variant. Although the expression levels of ER and PR tend to be lower in pleomorphic ILC than in classical ILC, the tumor behavior in this variant is determined by tumor size, tumor stage, and lymph node involvement, similar to that in other conventional breast cancer types [20].

Some of the poor prognostic parameters such as larger tumor diameter, lymph node positivity, histological grade, and the Ki-67 proliferation index were higher in the pleomorphic and signet ring cell variants of ILC than in the other variants (Table II). Furthermore, the rate of distant metastasis was higher and the survival outcomes were worse in the pleomorphic ILC group compared with the other groups.

In the present study, the rates of ER and PR positivity were >80% in all ILC variants. Several studies have reported that >90% of the pleomorphic ILCs are ER-positive, whereas other studies have found ER positivity rates of <80% [21-23]. Ciobanu et al [24]. found that pleomorphic ILC was observed in older patients and was detected at more advanced stages (stages III and IV); they also reported that pleomorphic ILC was associated with more frequent lymph node involvement than classical ILC. In addition, there were no significant differences in the hormone receptor and HER2 status between the two variants. In addition, there were no significant differences in hormone and HER2 status between the two subtypes [24]. In the current study, no significant difference was detected between the variants in terms of ER, PR, and HER2 status which are important prognostic factors. The mastectomy rate was high for all variants except for the tubulolobular variant, which might

be associated with the smaller tumor diameter in the tubulolobular variant as well as high multicentricity in other variants. There were no significant differences in the local and distant metastasis rates among the variants, although the survival rate was lower in the pleomorphic ILC than in the other ILC variants, which was consistent with previous studies reporting poor prognosis and survival associated pleomorphic ILC [25].

Membranous E-cadherin expression is present in approximately 10%-15% of all ILCs [17,26]. It is possible that ILCs with the typical morphology harbor E-cadherin mutations [17]; some non-lobular carcinomas lack E-cadherin expression [27]. In the current study, approximately 10% of all subsets exhibited E-cadherin expression.

Although invasive lobular carcinoma is considered a risk factor for bilateral breast cancer, there is a lack of literature about the relationship of the each subtypes of ILC and biletarality [28]. Besides, in our study the rarity of bilaterality among the subtypes couldn't enable us to draw a conclusion regarding this issue.

Limitations of the current study include the small sample size of the tubulolobular, solid, and signet ring cell variant groups, retrospective nature of the study, and that it was a single-center study.

The clinicopathological characteristics and patient outcomes differed among the ILC variants in the current study cohort, highlighting the potential benefit of individualized treatment according to the specific ILC variants owing to their complex behavioral patterns.

Moreover, the pleomorphic variant of ILC exhibits several adverse features, which should be considered during treatment planning.

Riassunto

L'incidenza del carcinoma lobulare invasivo (ILC), un tipo di carcinoma mammario comprendente diverse varianti con caratteristiche morfologiche e molecolari e comportamenti clinici distinti, è aumentata negli ultimi anni. A differenza del carcinoma lobulare classico ben definito, la variante ILC più comune, permangono alcune incertezze riguardo alle caratteristiche di altre varianti ILC. Pertanto, abbiamo studiato le caratteristiche clinicopatologiche e gli esiti di sopravvivenza di specifiche varianti ILC.

In questo studio retrospettivo sono state confrontate le caratteristiche e gli esiti del tumore e del paziente secondo specifiche varianti ILC in 77 pazienti sottoposte al trattamento chirurgico per ILC tra gennaio 2010 e dicembre 2016 in un singolo centro in Turchia.

Risultati: l'età media delle pazienti era di 54,58 ± 11,7 anni. Le varianti di ILC considerate erano a cellule classiche, a cellule pleomorfe, tubulolobulari, solide e con anello a sigillo, rispettivamente in 49 (63,6%), 14 (18,2%), 10 (12,8%), 2 (2,7%) e 2 (2,7%). Il diametro medio del tumore, il grado istologico, l'indice di proliferazione del Ki-67, la metastasi linfonodali, l'espressione della caderina E, l'invasione linfovascolare e il tipo di trattamento chirurgico sono state significativamente differenti tra le varianti. Tuttavia, non vi sono state differenze significative nei tassi di recidiva locale, metastasi a distanza e sopravvivenza globale tra le varianti.

Conclusioni: nonostante le buone caratteristiche prognostiche e la buona risposta al trattamento, diversi studi hanno riportato che l'ILC è associato a scarsi risultati a lungo termine. Pertanto, permangono sfide significative nella gestione dell'ILC. Anche se si ritiene che sia un tipo istologico specifico, l'ILC è eterogeneo clinicamente e patologicamente. Pertanto, l'identificazione di pazienti con scarse varianti prognostiche dovrebbe aiutare nell'implementazione di opzioni terapeutiche efficienti e personalizzate.

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