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Comparison of Clinicopathological Characteristics and Outcome of Inflammatoryand Non-inflammatory Locally Advanced Breast Cancer: A Study in Iran

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ABSTRACT

Background: Inflammatory breast cancer (IBC), a subgroup of locally advanced breast cancer (LABC), is diagnosed based on clinical findings, and seems to be different from other types of LABC. The purpose of this study was to compare clinicopathological characteristics and outcomes between inflammatory and non-inflammatory LABC patients at Breast Cancer Research Center (BCRC), Tehran, Iran.

Mehods: The medical records of all patients who were diagnosed as LABC in BCRC since 1997 to 2011 were extracted from the database. Then, clinical and pathological characteristics and overall survival of IBC patients were compared with non-inflammatory LABC (NI-LABC).

Results: A total number of 340 patients were identified as LABC from which 17 patients (5%) were diagnosed as IBC. Menopausal status, body mass index (BMI), family history of breast cancer, nodal status, and Her2/neu and PR positivity were not statistically different between IBC and NI-LABC groups. The difference in estrogen receptor (ER) between the two groups was significant (P = 0.028). Median duration of follow-up was 26.50 months. Patients with IBC had overall survival of 27.9 months (95% CI: 22.7–33.1) which was lower than patients in the NII-LABC group with a survival of 118.9 months (95% CI: 107.3-130.6) (P = 0.015). The difference between the disease-free survivals of the two groups were also statistically significant (P < 0.001).

Conclusions: Compared to NI-LABC, IBC is more frequently ER negative and more commonly associated with lower survival rate. These findings reinforce the idea that IBC has a more aggressive biology and more unfavorable outcome than NI-LABC and needs close follow-up

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Introduction

Locally advanced breast cancer (LABC) is a rare but clinically important type of breast cancer which is defined as primary breast cancer with skin or chest wall invasion (T4a-c), fixed axillary lymph nodes, ipsilateral supraclavicular, infraclavicular or internal mammary nodal involvement (N2-N3), or

inflammatory breast cancer (T4d).[1,2] In some developing countries, LABC comprises about 40–60% of diagnosed breast cancers; this percentage represents delayed diagnosis and management of breast cancer.[3,4]

Inflammatory breast cancer (IBC), as a subgroup of LABC, constitutes about 2.5% of all breast cancers.[5] The diagnosis of IBC depends on a combination of pathological confirmation of invasive carcinoma and a set of clinical findings including diffuse erythema and edema, usually without a palpable mass.[6] Several retrospective studies that compared patients with IBC and those with non-inflammatory LABC (NI-LABC) demonstrated that IBC is more aggressive.[7,8] Currently, the most common approach for management of LABC consists of neoadjuvant chemotherapy followed by surgery and radiation therapy.[4] Hormonal treatment is added to the regimen of receptor-positive patients and those with Her2/neu-positive disease would benefit from trastuzumab therapy.[4]

As there is little information about clinical features and survival of patients with LABC in Iran, we decided to compare the clinicopathological characteristics and survival between the IBC and NILABC subgroups.

Methods

Medical records of all patients diagnosed with LABC in Breast Cancer Research Center (BCRC), Tehran, Iran, from 1997 to 2011 were extracted from the electronic database and reviewed (n = 294). LABC was defined as clinical stage III breast cancer according to the American Joint Committee on Cancer (AJCC) Staging Manual.[9] IBC was diagnosed clinically according to the AJCC classification which requires erythema and edema involvong a third or more of the skin of the breast. Clinical data including tumor size, tumor stage, and number of involved lymph nodes were retrieved.

The parametric Student's t-test and one-way ANOVA were used to compare variables with normal distribution. The study variables that did not meet the required assumptions of normality were analyzed using the Mann-Whitney and Kruskal-Wallis tests. The main outcome variable was overall survival (OS) determined as the time from diagnosis until the date of death (from any cause) or the date of last follow-up visit (whichever occurred first), until the date of death (from any cause)? Overall and disease-free survival rates of the patients were compared by Kaplan-Meier analysis and the statistical significance was assessed using the log rank test. The level of statistical significance was defined as $P < 0.05$. Statistical analysis was performed using SPSS for Windows (version 15; SPSS Inc., Chicago, IL, USA).

Results

A total number of 294 patients were diagnosed as LABC, of which 17 patients (5.7%) had the IBC subtype.

The patients' characteristics are shown in table 1. The mean age of patients was 45.39 ± 10.10 years (range: 28–79). Clinical and pathological characteristics of the patients are presented in table 2. Invasive ductal carcinoma was the most common pathological type which was confirmed in 242 (86.1%) patients.

Table 1. Demographic characteristics of the patients (n = 68)

	Mean ± SD/ Number (%)
Age	45.39 ± 10.10
Age at menarche	13.45 ± 1.34
Age at menopause	47.20 ± 5.84
Age at first pregnancy	21.24 ± 5.37
BMI	28.92 ± 5.56
Family history of breast cancer	30 (10.3%)

Table 2. Clinical and Pathologic characteristics of the patients

	Number	(%)
Tumor size		
< 2 cm	16	(5.9%)
2-5 cm	123	(45.7%)
> 5 cm	93	(34.6%)
Chest wall or skin involvement	20	(7.4%)
Inflammatory cancer	17	(6.3%)
Lymph node involvement		
0	3	(1.0%)
1-3	40	(13.7%)
4-9	172	(59.1%)
> 9	76	(26.1%)
Grade		
I	27	(12.2%)
II	119	(53.8%)
III	75	(33.9%)
Stage		
IIIa	184	(62.6%)
IIIb	27	(9.2%)
IIIc	66	(22.4%)
Inflammatory	17	(5.8%)

Table 3 demonstrates clinicopathological characteristics of IBC and NI-LABC patients. Mean age of IBC patients was 47.94 ± 6.97 and for the NILABC was 45.69 ± 10.18 years. There was no significant difference between the two groups for body mass index (BMI), family history of breast cancer, lymph node status, tumor size, Her2/neu receptor, progesterone receptor (PR), and menstrual status. However, patients with IBC were more frequently diagnosed as ER negative compared to

Table 3. Comparison between inflammatory and non-inflammatory cases

	NI-LABC Mean ± SD/n (Percent)	IBC Mean ± SD/n (Percent)	P-value
BMI	28.83 ± 5.08	30.62 ± 11.11	0.228
Age			0.140
< 45	135 (48.7%)	5 (29.4%)	
⩾ 45	142 (51.3%)	12 (70.6%)	
Family history			0.383
Negative	243 (89.0%)	16 (94.1%)	
Positive	30 (11.0%)	1 (5.9%)	
ER			0.028
Negative	77 (33.5%)	8 (66.7%)	
Positive	153 (66.5%)	4 (33.3%)	
PR			0.132
Negative	94 (41.4%)	8 (66.7%)	
Positive	133 (58.6%)	4 (33.3%)	
Her2/neu			0.234
Negative	115 (65.3%)	6 (60.0%)	
Positive	61 (34.7%)	4 (40.0%)	
Lymph node involvement			0.724
0	3 (1.1%)	0 (0.0%)	
1-3	38 (13.7%)	2 (14.3%)	
4-9	162 (58.5%)	10 (71.4%)	
> 9	74 (26.7%)	2 (14.3%)	
Menopausal status			0.284
Pre-menopause	183 (67.0%)	14 (82.4%)	
Post-menopause	90 (33.0%)	3 (17.6%)	

NILABC group (P = 0.028)

Median follow-up duration was 26.50 months ranging from 1 to 160 months. Patients with IBC had overall survival of 27.9 months (95% CI: 22.7–33.1) which was lower than patients in the NI-LABC group with a survival of 118.9 months (95% CI: 107.3–130.6) (Figure 1). The mentioned difference was statistically significant (P = 0.015). Additionally, subjects who were diagnosed as IBC had a lower disease-free survival (DFS) of 20.5 (95% CI: 15.2–25.8) compared to those with NI-LABC who had DFS of 49.9 (95% CI: 44.5–55.2).

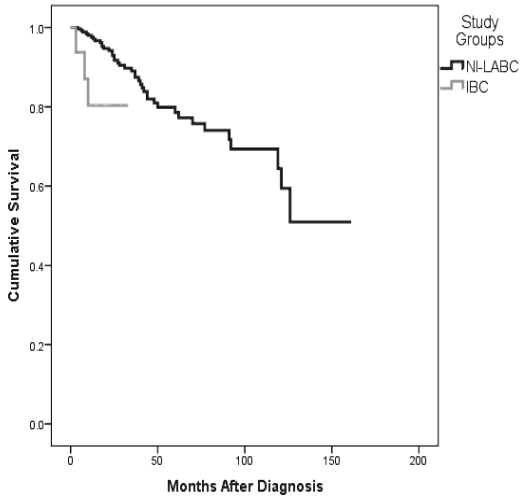

Figure 1. Overall survival (OS) analysis of LABC subtypes (P = 0.015)

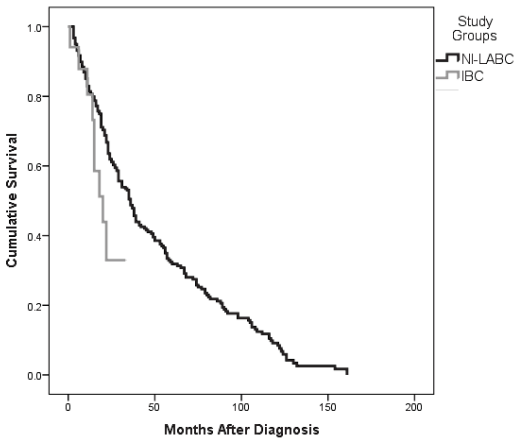

Figure 2. Disease-free survival (DFS) of patients with IBC compared to NI-LABC (P = 0.048)

The differences between DFS of the two groups were statistically significant (P = 0.048) (Figure 2).

Discussion

Based on the results of this study, IBC was more frequently ER negative in comparison to NI-LABC. Meanwhile, both DFS and OS of IBC patients were significantly lower than other LABCs (P = 0.048, P = 0.015, respectively).

As expected, IBC patients comprised a small proportion of LABC patients (5%). It should be considered that along with IBC rarity, the need to be detected clinically in addition to the pathological

diagnosis is also a cause of the low number of diagnosed IBC cases in breast cancer studies.[10]

Some studies have suggested a younger age at diagnosis of IBC in comparison to NI-LABC patients, but our study showed older age for these patients, although this difference was not significant.[10-13]

Although BMI is considered a potential risk factor for breast cancer, the higher BMI of IBC patients in the present study, similar to some other reports, was not significantly different from the NILABC group.[13-16]

Estrogen and progesterone receptors tend to be negative in IBC cases.11 Kokal *et al.* showed that patients with IBC have a significantly higher incidence of ER negative tumors in comparison to other groups of LABC.17 This was consistent with our findings.

Our study found no difference in Her2/neu expression between the two study groups. This lack of difference could be due to the small size of the IBC group in our study, which is considered a potential limitation in similar studies. Controversy remains in literature regarding Her2/neu expression and IBC; while some studies with a high number of IBC cases did not detect a significant difference in Her2/neu expression, others showed higher Her2/neu expression in IBC patients.[18-20]

In the present study, survival of the patients with the same therapeutic regimens, showed a significantly lower DFS (20.52 vs. 49.90) and OS (27.91 vs. 118.99) for IBC patients. A similar study in Turkey did not find a significantly lower survival rate in patients with IBC.[13] Most studies comparing IBC with NI-LABC have demonstrated poor prognostic outcomes for IBC compared with NILABC. [21] This finding reinforces the idea of IBC having a distinct biological behavior.

Compared to NI-LABC, IBC is rare, more frequently ER negative, and more commonly associated with lower survival rate. These findings reinforce the idea that IBC has a more aggressive biology and more unfavorable outcome than NILABC and necessitates close follow up.

Conflict of interests

The authors have declared no conflicts of interest.

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