



Comparison of Outcome between Invasive Lobular Carcinoma (ILC) and Invasive Ductal Carcinoma (IDC) Patients Treating with Breast Conserving Surgery (BCS) and Radical Dose of Intraoperative Electron Radiotherapy (IOERT)

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Abstract

Background: Invasive lobular carcinoma (ILC) differs from invasive ductal carcinoma (IDC) in genomic profile, clinicopathologic behavior, and response to treatment. Despite favorable profile, ILC is susceptible to recurrence. Thus, most of studies did not include ILC in intraoperative radiotherapy (IORT) trials or considered it as a cautionary criteria, especially in accelerated partial breast irradiation (APBI).

Objectives: In this study, we compared treatment outcome between breast cancer patients with ILC and IDC treating with breast conserving surgery and intraoperative electron radiotherapy (IOERT).

Methods: A total of 191 patients with early breast cancer treated with breast conserving surgery and IOERT were included in the study. This study compared outcome of 42 ILC patients with 135 IDC patients. Fourteen patients were mixed type. ILC was a suitable criterion, as well. Local recurrence and disease-free survival were endpoints of study.

Results: Median follow-up was 23.17 month and 21.17 month for IDC and ILC, respectively. Univariate analysis was done according to age, pathologic, and biologic factors and multivariate analysis was according molecular subtype. There were 3 patients with local recurrence. Two patients were in the IDC group and another one was the ILC group. There was no significant difference between two groups. The 4-year disease-free survival (DFS) was 95.45% and 97.40% for ILC and IDC, respectively.

Conclusions: In this study, there was no significant difference in in-breast tumor recurrence (IBTR) and DFS between two groups. It was seem lobular carcinoma can be used for APBI and it may be a suitable criterion as the IDC.

Keywords: Breast Cancer, Intra Operative Radiotherapy, Lobular Carcinoma, APBI, IOERT, Radical Dose

1. Background

Invasive breast cancer is a heterogenous disease. This is important about responses to therapy. Invasive ductal carcinoma (IDC) is the most common type of breast cancer and accounts for 70% to 80% of them (1). Invasive lobular carcinoma (ILC) and mixed type (IDC+ILC) constitute 5% to 15% and 3% to 5%, respectively (1).

ILC is a distinct pathology that differs from IDC in risk factors, histologic features, genomic profiles, immunophenotype, and response to systemic therapy (2). Besides, ILC typically does not destroy anatomic structures or stimulate tissue responses. Thus, there is no clinically

palpable mass and mammographic appearance is indistinct. Again, ILC has greater tendency for multicentricity and multifocality (3, 4). In fact, the extent of the disease can be underestimated. There is concern with local therapeutic approaches such as, accelerated partial breast irradiation (APBI) (5, 6). It should be remembered that the reliable margin is one of the most important intraoperative radiotherapy (IORT) selection criteria.

Accordingly, ILC is placed as a cautionary criteria in the American and the European guidelines for IORT (7, 8).

The incidence of ILC is increasing (9, 10). Nevertheless, although ILC tumor size is slightly large, that is found in elderly women with a low grade, a low proliferation rate in-

dex, and positive hormone receptor (11, 12). These features made it suitable for IORT. Thus, the percentage of patients treated with IORT is high.

Various results have been reported about ILC clinical outcome after IORT. Some studies have reported excellent clinical outcome after APBI for ILC. Despite a favorable features, ILC is suggested to use cautiously.

2. Objectives

The current study compares in-breast tumor recurrence (IBTR) and clinical outcome of ILC versus IDC in early breast cancer treated with radical IORT and evaluate ILC as a suitable criterion for radical IORT.

3. Methods

A total of 191 patients with early breast cancer (ductal and lobular) were treated with breast conserving surgery and radical IORT (21 Gy) in Cancer Research Center of Shahid Beheshti University of Medical Sciences (2013 - 2017). IORT was done by a specially designated mobile linear accelerator delivering energy levels of electrons (4 to 12 MeV) via a head maneuvered by a robot arm (Liac Deliver).

Primary end point was local recurrence incidence either tumor bed or axilla. Local recurrence incidence was calculated from surgery date to recurrence date or the last follow-up date.

Secondary end point was disease-free survival (DFS) and it was evaluated, using the Kaplan-Meier method.

Pure IDC (135), ILC (42), and mixed type (14) were designated in this survey. Technical IORT parameters did not differ between the subtypes and ILC like IDC was a suitable criterion for radical IORT (Table 1). The log-rank test was used for testing the equality of survival distributions for IDC and ILC.

The data of each group were analyzed according to age, tumor size, molecular characteristics, adjuvant therapy, and follow-up. Clinical outcomes, including IBTR and DFS, were analyzed.

Univariate and multivariate Cox regression analysis were done and influence of tumor characteristics were evaluated. Molecular subtype analysis for estrogen receptor (ER), progesterone receptor (PR), Ki67 and human epidermal growth factor receptor 2 (HER2) expression were done as multivariate analysis.

This study was approved by ethical committee of Shahid Beheshti University of Medical Sciences.

4. Results

Median follow-up was 23.17 months for IDC patients and 21.17 months for ILC patients. The results of Mann-Whitney test shows that there is no significant difference in median follow-up between two group ($P = 0.634$).

Table 1. Clinical, Pathologic, and Molecular Subtype Related Characteristics for the ILC and IDC Group.

Characteristics	Non-Lobular	Lobular
Total	135 (70.7)	56 (29.3)
Age		
< 40	0 (0)	1 (1.8)
40 - 44	3 (2.2)	5 (8.9)
≥ 45	132 (97.8)	50 (89.3)
Tumor Size		
< 3	115 (85.8)	49 (87.5)
3 - 3.5	17 (12.7)	7 (12.5)
> 3.5	2 (1.5)	0 (0)
Grade		
1	21 (16.2)	13 (23.6)
2	71 (54.6)	36 (65.5)
3	38 (29.2)	6 (10.9)
LVI		
Positive	16 (12.5)	4 (7.3)
Negative	112 (87.5)	52 (92.7)
ER		
Positive	110 (82.7)	52 (92.9)
Negative	23 (17.3)	4 (7.1)
PR		
Positive	104 (78.8)	51 (91.9)
Negative	28 (21.2)	33 (17.6)
Her2		
Positive	8 (6.0)	2 (3.6)
Negative	125 (94.0)	54 (96.4)
KI67		
< 20%	77 (58.8)	40 (71.4)
20% - 30%	31 (23.7)	9 (16.1)
> 30%	23 (17.6)	7 (12.5)
Luminal		
Luminal A	61 (45.9)	25 (44.6)
Luminal B	53 (39.8)	28 (50.0)
HER2 positive	3 (2.3)	1 (1.8)
Triple negative	16 (12.0)	2 (3.6)

^a Values are expressed as No. (%).

Median age of patients was 60 years for the IDC and 57.28 for the ILC and 57.7 for the mixed type.

Although, median age of ILC was less than IDC, percent patients ≥ 70 years, was similar to IDC (IDC = 17.7% vs. ILC = 16.06%). Nevertheless, just 10% of the patients with ILC were

under 45 years old.

Compared to IDC group, patients with ILC were lower grade (G1, 2; 87.8% vs. 71.1%), less lymphovascular invasion (92.7% vs. 87.5%), high hormonal status (ER, 92.9% vs. 82.7% -PR, 95.2% vs. 78.8%), greater HER2 negativity (100% vs. 94%), and lower proliferation index (Ki67 \geq 30%, 11.9% vs. 17.6%) (Table 1).

In two groups, tumor sizes were alike except, the ILC was not over 3cm.

There are two patients with recurrence in IDC group (one patients with local recurrence and the other one systemic recurrence) and one local recurrence in ILC patients (Table 2).

Table 2. Local Recurrence Indicator

Pathology	Recurrence Indicator		Total
	No	Yes	
IDC			
Count	134	1	135
% within pathology	99.2	0.74	100.0
ILC			
Count	41	1	42
% within pathology	97.6	2.4	100.0
IDC/ILC			
Count	14	0	14
% within pathology	100.0	0.0	100.0
Total			
Count	188	3	191
% within pathology	98.4	1.6	100.0

In the multivariate analysis, ER, PR, Ki67, and HER2 expression were represented by molecular subtype (Luminal A, Luminal B, HER2 positive, triple negative). Compared to the IDC group, patients with ILC were Luminal A (44.6% vs. 45.9%) and Luminal B (50% vs. 39.8%) rather than HER2 positive (1.8% vs. 2.3%) and triple negative (3.6% vs. 12%) (Table 3 and Figure 1).

The results of Cox regression analysis showed that the AHR for lobular patients compared to non-lobular patients was 1.34 (95% CI: 0.12 - 14.73; P = 0.813). So, there is no significant difference in the risk of recurrence between lobular and non-lobular patients.

Also, there is no difference in survival distributions for the different levels of pathology. The two years DFS is 100% for lobular and 99.05% for IDC patients. The 4 years DFS is 95.45% for lobular and 97.40% for IDC patients. Therefore, there is no statistical difference in DFS of two groups within 2 years and 4 years (Tables 4 and 5 and Figure 2).

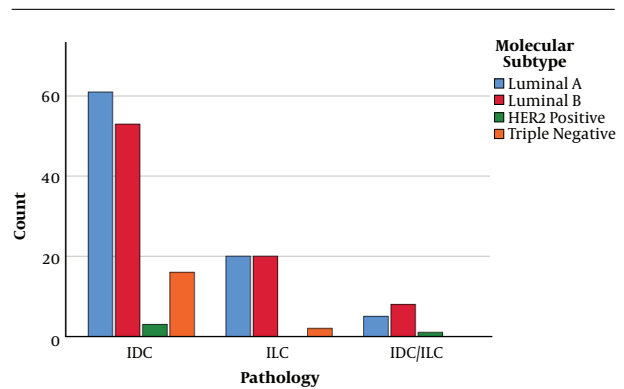


Figure 1. Molecular subtype in two groups.

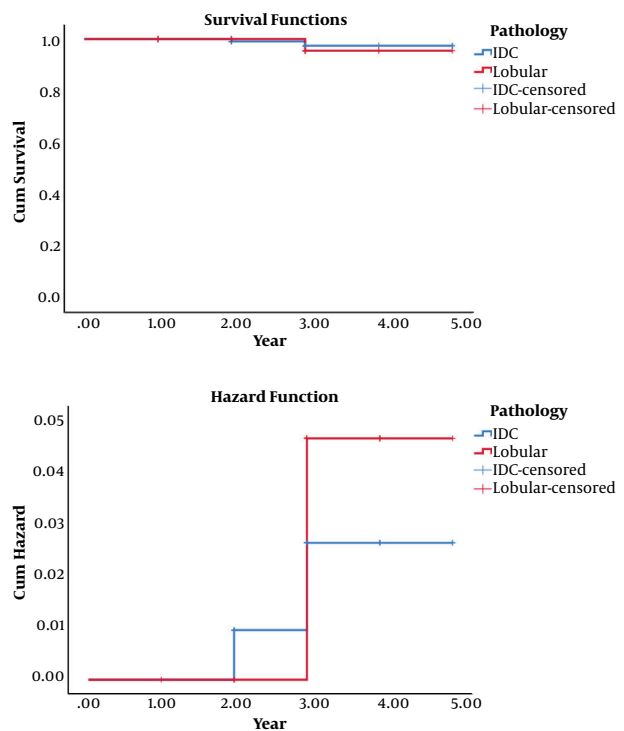


Figure 2. DFS and hazard function in two groups.

5. Discussion

In the present study, women with early breast cancer were treated with the IOERT for comparing the rate of local recurrence of ILC and IDC at the median follow-up of 23.17 and 21.7 month, respectively. There was no evidence of difference regarding local recurrence. Overall survival and disease-free survival did not differ between two groups.

As previous studies (13, 14) showed, lobular carcinoma was more likely to be ER-PR positive, low to be LVI positive, and to be absent HER2. Also, despite a less aggressive bi-

Table 3. Molecular Subtype of Two Group

Pathology	Molecular subtype				Total
	Luminal A	Luminal B	HER2 Positive	Triple Negative	
IDC	61 (45.9)	53 (39.8)	3 (2.3)	16 (12)	133
IILC	20 (44.6)	20 (50)	1 (1.8)	2 (3.6)	42
IDC/IILC	5	8	0	0	14
Total	86	81	4	18	189

Table 4. Means and Medians for Survival Time

Pathology	Mean ^a				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
IDC	4.938	0.043	4.854	5.023	-	-	-	-
Lobular	4.909	0.089	4.735	5.083	-	-	-	-
Overall	4.931	0.039	4.854	5.008	-	-	-	-

^a Estimation is limited to the largest survival time if it is censored.

Table 5. Test of Equality of Survival Distributions for the Different Levels of Pathology

Type of Test	Overall Comparisons		
	Chi-Square	df	P Value
Log rank (Mantel-Cox)	0.057	1	0.812
Breslow (Generalized Wilcoxon)	0.001	1	0.971
Tarone-Ware	0.011	1	0.918

ologic phenotype, recurrence and survival were similar to IDC patients.

Prior studies afford to consider ILC as a cautionary criteria in normal routine and again APBI guidelines (15, 16). So, the most of studies like randomized trial of accelerated partial breast irradiation (RAPID), targeted intraoperative radiotherapy (TARGIT) (12, 17), and IMPORT LOW (18) did not include patients with ILC on trials. Besides, ILC patients were registered in other studies as ELIOT (19), IRMA, and Groupe Européen de Curiethérapie -European Society for Radiotherapy and Oncology (GEC-STERO)- (17, 20), while the most of them did not report any association between local recurrence and histologic type.

In Leonardi et al. study (21), patients with ILC (252; 11.6%) were compared to those with IDC (1921; 88.4%). The 5 and 10 years IBTR rate were 7.5% and 21.8%, respectively, for ILC patients versus 5.5% and 14.4%, respectively, for IDC patients. They declared patients with ILC can be used for APBI with caution.

We contrasted 42 patients with ILC to 135 patients with IDC. The 2 years DFS is 100% for lobular and 99.05% for IDC patients. Also, 4 years DFS was 95.45% and 97.40%, respectively. So, there was no statistical difference between two groups.

Many of literature about ILC reported low grade, absence of lymphovascular invasion, positive expression of hormone receptors, greater HER2 negativity, and occurrence in older patients (13, 14). Our patients with ILC were younger. It may be due to youth population of area. Our patients with ILC had low risk profile, as well. They were as young as patients with IDC.

Multivariate analysis was according to molecular subtype. Perhaps, multivariate analysis demonstrated better biologic behavior for ILC. Whereas, 44.6% of the patients with ILC were Luminal A versus 45.9% of the patients with IDC; other subtypes included Luminal B (50% vs. 39.8%), HER2 positive (1.8% vs. 2.3%), and triple negative (3.6% vs. 12%), respectively.

Table 6 shows that there is no significant difference in hazard ratio between two groups with respect to their covariate values. Hazard ratio for Luminal B is 3.419; it means the HR of Luminal B is 3.419 times more than other subtypes. As regards high percentage of Luminal B in ILC patients, it seems lobular pathology is susceptible to IBTR, whereas there is no statistical significance.

Table 6. Hazard Ratio between ILC and IDC Patients, According to Clinical, Pathologic, and Treatment Related Characteristics (Stratified Analysis)

Characteristics	Beta	Standard Error	HR	95% CI	P Value
Age					
< 40					
40 - 44	-3.098	11.835	0.045	(0.000, 5E+09)	0.794
≥ 45	3.098	11.835	22.147	(0.000, 2E+11)	0.794
Tumor Size					
< 3	3.276	7.097	26.474	(0.000, 2E+08)	0.644
3 - 3.5	-3.239	7.435	0.039	(0.000, 8E+05)	0.663
> 3.5	-3.035	21.120	0.048	(0.000, 4E+16)	0.886
Grade					
1	-3.344	6.409	0.035	(0.000, 1E+05)	0.602
2	4.171	4.758	64.771	(0.010, 7E+06)	0.381
3	-3.664	5.377	0.026	(0.000, 966)	0.496
LVI					
Positive	1.280	1.241	3.598	(0.316, 40.498)	0.302
Negative	-1.280	1.241	0.278	(0.024, 3.164)	0.302
ER					
Positive	3.234	7.478	25.384	(0.000, 5E+08)	0.665
Negative	-3.234	7.478	0.039	(0.000, 9E+05)	0.665
PR					
Positive	3.354	6.212	28.614	(0.000, 5E+07)	0.589
Negative	-3.354	6.212	0.035	(0.000, 6E+04)	0.589
Her2					
Positive	-3.141	11.369	0.043	(0.000, 2E+9)	0.782
Negative	3.141	11.369	23.120	(0.000, 1E+11)	0.782
KI67					
< 20%	-1.177	1.228	0.308	(0.028, 3.422)	0.338
20% - 30%	0.591	1.232	1.805	(0.161, 20.175)	0.632
> 30%	0.928	1.225	2.528	(0.229, 27.892)	0.449
Luminal					
Luminal A	-0.726	1.226	0.484	(0.044, 5.348)	0.554
Luminal B	1.229	1.230	3.419	(0.307, 38.079)	0.317
HER2 positive	-3.054	17.667	0.047	(0.000, 5.2E+13)	0.863
Triple negative	-3.161	8.509	0.042	(0.000, 7.4E+6)	0.710

5.1. Conclusions

Many of studies, which included lobular carcinoma on trial, did not report by histology. So, the current study not only did it, but also registered the ILC as a suitable criterion in the survey. According to the results, there was no significant difference in IBTR and DFS between two groups. It seems lobular carcinoma can be used for APBI and it may be a suitable criterion as the IDC. This study evaluated patients on 4 years and follow-up period was not long. Thereafter, it is better the study go on in the future and more accurate results would be reported.

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Footnotes

Authors' Contribution: None declared.

Conflict of Interests: None declared.

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