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# Outcome of Management of Invasive Lobular Carcinoma in Comparison to Invasive Duct Carcinoma

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## Abstract

**Background:** Among females, breast cancer has the highest incidence and is the leading cause of cancer-related death globally.

**Aim:** In contrast to invasive lobular carcinoma (ILC), the objective of this research is to examine how invasive duct carcinoma (IDC) is managed.

**Patient and methods:** This examined 200 women who were registered in the Al-Azhar University Hospitals database between January 2020 and December 2022 and were diagnosed with nonmetastatic invasive breast cancer. The current investigation included cases with IDC or ILC histology based on the WHO classification's criteria.

**Results:** The patient met the criteria for M0 illness by undergoing primary curative breast surgery, of which 170 (85%) were classified as IDC and 17 (8.5%) as ILC. The remaining patients were ruled out of further research due to their diagnosis of different histological subtypes, 13 of which had mixed ILC and IDC. Cases with ILC were offered mastectomy more often than those with IDC (79.4 vs. 67.7%). ILC cases had lower levels of human epidermal growth factor receptor 2 positivity (9 vs. 18%) but higher levels of estrogen receptor-positive illness (83 vs. 70%) and progesterone receptor-positive disease (75 vs. 60%) when compared with IDC individuals.

**Conclusion:** ILC has unique biologic and prognostic characteristics that may call for various treatment modalities.

**Keywords:** Breast cancer, Clinical outcome, Egyptian women, Invasive duct carcinoma

## 1. Introduction

Breast cancer is the preponderant cause of cancer-related mortality among women between the ages of 20 and 59, and it is the most prevalent reason for this outcome. Breast cancer accounts for around 1/3 (33%) of all cancer cases among females and contributes to ~1/5 (20%) of cancer-related deaths. According to statistical data from 2008, breast cancer was projected to be the most prevalent form of cancer among women in Egypt, accounting for 37.7% of all reported cancer cases. This amounted to a total of 12,621 newly diagnosed cases. With a total of 6546 fatalities, it stands as the primary contributor to cancer-related mortalities, representing 29.1% of the overall count.<sup>1</sup>

Invasive breast cancer comprises two predominant histological subtypes, namely infiltrating ductal carcinoma and infiltrating lobular carcinoma. Invasive ductal carcinoma (IDC) is observed in about 75% of patients, rendering it the most prevalent subtype.<sup>2,3</sup>

Treatment guidelines for breast cancer are mostly derived from the outcomes of cases with IDC, which represents a significant majority of the global breast cancer population. At now, the treatment recommendations for both invasive lobular carcinoma (ILC) and IDC subtypes are similar, mostly based on the stage and phenotype of the disease. However, the possible influence of histological subtypes is not yet considered in these recommendations. The user's text is too brief to be rewritten academically.

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During the presentation, the detection of ILC poses challenges in both clinical and radiological assessments. This phenomenon is correlated with a heightened tendency for the spread of several centers and the occurrence of bilateral manifestations.<sup>4</sup>

Thus, this retrospective research was undertaken to examine the epidemiology, pathological characteristics, and prognosis of ILC among breast cancer cases in Egypt. Additionally, a comparative analysis was performed to evaluate the concordance of these findings with those reported in other global regions.<sup>5</sup>

The field of breast cancer surgery has witnessed significant advancements, transitioning from extensively radical and incapacitating procedures to less invasive techniques. Moreover, there has been a notable shift from disfiguring interventions to the attainment of reconstructive brilliance.<sup>6</sup>

One of the primary goals of neo-adjuvant chemotherapy (NACT) in the context of breast tumors is to render an initially inoperable tumor amenable to surgical intervention. In patients of this nature, NACT can facilitate the attainment of suitable disease management that would otherwise be unattainable only through surgical intervention. In addition, it is possible to effectively treat patients by employing breast-conserving surgery subsequent to NACT.<sup>7</sup>

### *1.1. The treatment modalities for breast cancer encompass surgical interventions and pharmacological approaches*

The surgical intervention known as Mastectomy, which involves the removal of the breast, is widely regarded as the standard method for addressing ipsilateral local recurrence following conservative surgery. This approach was favored by 65% of respondents. Alternatively, 32% of respondents expressed a preference for undergoing another Breast-Conserving Surgery (BCS) and subsequently receiving radiation, but only if the lead time exceeded 5 years. There are certain factors that may support the implementation of a BCS. These factors include the presence of low-risk tumors, namely small, luminal A tumors, which have a favorable prognosis in around 75% of cases. Additionally, an intermediate risk factor for a second BCS is the passage of a 5-year interval since the initial diagnosis, which is associated with a 72% likelihood of success.<sup>8</sup>

Additionally, it is common practice to perform Axillary lymph node dissection (ALND) following neoadjuvant therapy in cases where macrometastasis is present, as evidenced by a 63% occurrence rate. However, the International Breast Cancer

analysis Group (IBCSG) 23–01 trial has had a significant impact on decision-making in cases of micrometastasis, with 57% of individuals being influenced by the trial and consequently opposing ALND. Conversely, 27% of voters agreed to proceed with dissection in such cases. When isolated tumor cells (ITCs) are present, the sentiment is divided, with 10% in favor of ALND and 43% against it. Finally, in cases where 1–3 positive sentinel lymph nodes (SLN) are present, the majority (72%) support ALND, while 28% are opposed. It is advisable to refrain from performing axillary surgery in cases where the patient's age exceeds 70 years, as this was observed in 46% of the cases. A quarter of the panel expressed a preference for avoiding axillary surgery solely in patients aged 80 years and beyond, whereas 23% held the belief that age should not be considered as a determining factor for omitting axillary surgery.<sup>4,9,10</sup>

Neoadjuvant therapy, namely pathological complete response, has been seen as a surrogate goal for the approval of drugs in the context of early-stage breast cancer. When questioned about the aforementioned remark, a majority of 59% of the panel expressed their support for this method, provided that the treatment regimens administered resulted in a significant enhancement in pathological complete response rates, namely a 50% increase compared with the control group.<sup>7,10</sup>

The panel was presented with the choice of selecting an appropriate adjuvant endocrine therapy for hormone receptor-positive patients. Specifically, they were asked to consider the threshold level for estrogen receptor (ER) positivity, with options of greater than or equal to 1% or greater than or equal to 10% as determined by immunohistochemistry. The panel was evenly divided, with a 50/50 split in their preferences. However, the majority of votes (97%) recommended endocrine treatment for patients with any tumor size, including those with microinvasive disease, who exhibit luminal A and B-like lesions.<sup>11</sup>

In situations of premenopausal individuals with luminal A-like tumors and positive lymph node disease, a majority of 99% of voters expressed agreement with the notion of extending endocrine therapy beyond the standard 5-year duration. Among these voters, 34% advocated for an extra 2–3 years of treatment, while 65% supported a total treatment duration of 10 years.<sup>12,13</sup>

The panel's consensus on the matter of Endocrine adjuvant treatment in postmenopausal instances indicates that a significant majority (94%) agreed that patients with stage less than or equal to II, positive ER, negative HER2 disease, and low-risk

signature assays (such as recurrence scores  $\leq 25$ ) should not be administered chemotherapy. In cases when there is an advanced anatomical stage (pT3, N1, or  $>3$  infiltrated lymph nodes), a significant majority of 97% of respondents opted to administer chemotherapy, while a mere 3% indicated a decision to abstain from its use.<sup>12</sup>

There is a growing body of research suggesting that aggressive metastasis-directed therapy, including as surgery and/or hypo fractionated treatment, may be beneficial for patients with oligometastatic breast cancer. Oligometastatic illness is often characterized by the presence of five or fewer metastases as detected through imaging.<sup>13</sup>

The objective of this trail was to examine the outcomes of managing ILC in comparison with IDC.

## 2. Patient and methods

A retrospective research of the Al-Azhar University Hospitals database revealed 200 female patients with nonmetastatic invasive breast cancer. The study period encompassed January 2020 to December 2022. The current investigation comprised patients who met the criteria outlined by the WHO classification and had histology consistent with IDC or ILC. Histological subtypes such as mixed ILC and IDC were not considered in this study. All patients who met the criteria underwent primary curative surgery for their respective medical condition.

Therefore, the luminal subtypes of breast cancer were determined by employing immunohistochemistry surrogates that relied on the assessment of ER, progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) expressions. The Luminal A group, characterized by a favorable prognosis, is defined by the presence of ER, PgR, and HER2 negativity. On the other hand, the Luminal B group, associated with a poor prognosis, is characterized by ER positivity, PR negativity, and either HER2 negativity or HER2 positivity with any level of PgR expression.

In accordance with the treatment protocols implemented at our institution during the designated study period, patients diagnosed with ILC and IDC were administered adjuvant chemotherapy, endocrine or anti-HER2 therapy, and radiotherapy in an equitable manner.

Obtaining formal approval from an ethics committee was not deemed necessary for the execution of this retrospective analysis. Nevertheless, the management of data and the preservation of patient anonymity were performed in accordance with the principles delineated in the Declaration of Helsinki.

### 2.1. Statistical analysis

The patients' demographic and clinical characteristics were evaluated with the help of a descriptive statistical analysis.  $\chi^2$  analysis was used to see if there was a significant association between individual patient and tumor characteristics and pathological subtype. This research looked at the overall frequency of breast cancer-related occurrences like regional recurrence, metastasis, and a second primary tumor developing on the opposite side of the body. The major purpose of this research was to estimate disease-free survival (DFS), which was defined as the period among the surgical procedure and the incidence of any breast cancer-related events specified earlier, death from any cause, or the last follow-up date. Using the data we had, we constructed survival curves. It is about the years 15 and 16. SPSS (version 24) was utilized for the statistical analysis.

## 3. Results

### 3.1. Patient characteristics

During the timeframe spanning from 2020 to 2022, our database recorded a total of 200 female individuals who underwent primary curative breast surgery for M0 illness. Among these cases, 170 individuals (85%) were diagnosed as having IDC, whereas 17 individuals (8.5%) were classified as having ILC. The remaining cases were identified as having different histological subtypes, which included 13 instances with a combination of ILC and IDC. These cases were subsequently eliminated from any additional investigation, [Table 1](#).

The median age of the two groups was 50 years, although the percentage of patients with ILC who were diagnosed before the age of 35 was significantly lower (3.4 vs. 9.3% with IDC;  $P = 0.009$ ). Patients with ILC experienced bilaterality at presentation at a higher rate (4% vs. 1%, correspondingly;  $P = 0.001$ ) than patients with IDC. The T stage was higher in ILC patients (20.3 vs. 13.4%;  $P = 0.027$ ) and the positive nodal involvement was higher (67.3 vs. 60%;  $P = 0.004$ ).

Table 1. Histological subtypes.

Pathologic subtype	Number (%)
Pure IDC	170 (85)
Pure invasive lobular carcinoma	17 (8.5)
Mixed ductal and lobular†	5 (2.5)
Medullary†	3 (1.5)
Others subtypes or unknown†	5 (2.5)
Total	200 (100)

Participants with ILC were offered mastectomy more often than those with IDC (79.4 vs. 67.7%). ILC patients had lower levels of HER2 positivity (9 vs. 18%), but higher rates of ER-positive illness (83 vs. 70%) and PgR-positive disease (75 vs. 60%) as compared with IDC patients. Less unfavorable luminal phenotypes (8.1 vs. 16.9%) and less HER2-enriched illness (2.7 vs. 11.5%) were both substantially correlated with ILC, [Table 2](#).

### 3.2. Follow-up and survival analysis

100 cases with IDC (40%) and 55 cases with ILC (30%) had relapsed at a median follow-up period of 64 months (range 28–122 months) ( $P = 0.019$ ); 6 patients with ILC (4%) and 76 patients with IDC (4%) had developed contralateral illness, [Table 3](#).

Lung metastases were more common in patients with IDC than in patients with ILC among relapsing patients (6 vs. 30%;  $P = 0.036$ ). However, the

incidence of peritoneal/ovarian metastases (3 vs. 5%, respectively;  $P = 0.001$ ) and bone metastases (35 vs. 50%;  $P = 0.002$ ) was higher in individuals with ILC. Throughout the follow-up period, there was no variation in the occurrence of contralateral disease evolution among the 2 groups (4.3% in IDC and 3.4% in ILC), [Table 4](#).

## 4. Discussion

In this study of considerable scale, it was found that ILC accounted for 8.5% of breast cancer cases among Egyptian women. Studies conducted in the Middle East region have yielded findings regarding the occurrence of ILC in Turkey and Israel, with reported rates of 12 and 10.9%, respectively.<sup>14</sup>

The majority of Far East countries, such as Japan and Korea, have reported a far lower incidence rate, ranging from ~2–4%.<sup>14</sup> Studies conducted in Western countries have observed a comparatively

*Table 2. The clinicopathological features based on the histologic subtype.*

Clinic pathological parameter	Histologic subtype		P-value
	Invasive lobular carcinoma (%)	Invasive ductal carcinoma (%)	
Number of patients	100	100	
Age			
Median (range)	55 (24–78)	60 (24–88)	
Years	4%	20	0.009
Menopausal status			
Premenopausal	47%	45%	0.441
Postmenopausal	53%	55%	
Bilaterality at presentation			
Present	5%	2%	0.001
Surgery			
BCS	21%	33%	
MRM	79%	67%	0.002
Pathological T stage at presentation			
T1 and T2	80%	85%	0.027
T3 and T4	20%	15%	
Pathological N stage at presentation			
N0	33%	40%	0.004
N+	67%	60%	
ER			
Negative	17%	30%	<0.001
Positive	83%	70%	
Missing	12	165	
PgR			
Negative	25%	40%	<0.001
Positive	75%	60%	
HER2			
Negative	82%	65%	<0.0001
Positive	9%	18%	
IHC 2+	9%	17%	
IHC subtypes			
ER+/PgR+/Her2-	70%	55%	<0.001
ER ± PgR+/Her2+ OR	9%	17%	<0.001
ER+/PgR-/Her2-	4%	13%	
Her2 enriched (ER-, PgR-, Her2+)	7%	13%	<0.001
Triple negative (ER-, PgR-, Her2-)	10%	12%	0.160

BCS, Breast conservative surgery; MRM, Modified radical mastectomy.

Table 3. Events of disease-free survival according on histology (invasive lobular carcinoma as opposed to invasive ductile carcinoma).

Disease-free survival events <sup>a</sup>	Invasive lobular carcinoma		Invasive ductal carcinoma		P = value
	Number	% of relapsed patients	Number	% of relapsed patients	
Total relapses <sup>c</sup>	30 (30) <sup>b</sup>	NA	20 <sup>b</sup>	NA	0.019
Loco-regional recurrence	10 (5.7 of total ILC)	10	9 (9 of total IDC)	9	NS
All visceral relapses	25	25	55	55	NS
Lung relapse	6	6	30	30	0.036
Bone relapse	35	35	50	50	0.002
Peritoneum/ovarian relapses	3	3	5	5	0.001
2-Contra-lateral disease	4	NA	4 (4.3 of total IDC)	NA	NS

NA, Not applicable; NS, Not significant.

<sup>a</sup> DFS events include all locoregional and systemic relapses of the primary disease(s) and the contralateral disease evolution.

<sup>b</sup> % Does not add to 100% as many patients had more than one site of relapse.

<sup>c</sup> Includes locoregional recurrence.

Table 4. Multivariate analysis to ensure survival free from illness.

	Hazard ratio	95% CI	P-value
Age (<35 vs. >35 years)	0.92	0.59–1.53	0.795
Pathology (ILC vs. IDC)	0.59	0.37–0.94	0.023
T (<5 vs. ≥5 cm)	1.96	1.45–2.72	<0.001
N (N0 vs. N+)	1.72	1.47–2.02	<0.001
IHC subtype (LA vs. others)	0.88	0.78–0.97	0.008

HR, Hazard ratio; LA, Luminal A subtype; N, Pathological nodal status; N+, Positive axillary lymph node involvement; N0, Negative axillary lymph node involvement; T, Pathological tumor size.

low occurrence of ILC, ~6%, among individuals diagnosed prior to the 1990s.<sup>2</sup>

Nevertheless, new data continuously indicate a greater prevalence of ILC ranging from 10 to 15%. This observed increase has been linked to the escalated utilization of hormone-replacement treatment during the past twenty years, which seems to elevate the chance of developing ILC to a greater extent compared with other histologic subtypes.<sup>15</sup>

Hence, although no particular racial or ethnic predisposition for ILC has been proposed, it appears that lifestyle factors such as hormone replacement medication and postponed child-bearing are among the most significant risk factors associated with the development of this specific histologic subtype.<sup>16</sup>

In our study, ILC was found to be correlated with a higher T stage in comparison to IDC, a finding that has been consistently documented in previous research. The diagnosis of ILC often experiences delays due to the challenges correlated with its clinical and radiographic detection. This difficulty arises from the distinct diffuse growth pattern of ILC inside the breast parenchyma.<sup>17</sup>

A considerable proportion of patients in our study, almost 70%, underwent mastectomy, a

notably larger percentage compared with data sets from Western sources.<sup>15,16</sup>

In the present investigation, it was found that there was no discernible rise in the incidence of local relapse among the relatively small cohort of individuals diagnosed with ILC who underwent BCS in comparison to those who underwent mastectomy. A higher prevalence of disease bilaterality was identified in individuals with ILC, a finding that has also been documented in previous research.<sup>16</sup>

Nevertheless, the ILC group did not exhibit any additional rise in contralateral illness. This finding aligns with a recent comprehensive analysis conducted by IBCSG, which involved 767 instances of ILC and 8607 cases of IDC. The study revealed that the 20-year incidence of contralateral breast cancer was 8.1% for ILC and 5.7% for IDC.<sup>2</sup>

In agreement with other studies<sup>16</sup> it was shown that lobular histology exhibited a notably reduced occurrence of lung metastasis, while demonstrating a heightened occurrence of bone and peritoneal relapses (Table 3). Our data also aligns with the prevailing consensus that ILC is associated with a notably increased occurrence of favorable luminal breast cancer phenotype. Through the utilization of gene expression profiling, it has been observed that the majority of ILC are classified under the luminal-A molecular subtype, accounting for ~75% of cases. Subsequently, the luminal-B subtype encompasses around 20% of ILCs. However, it is worth noting that certain ILCs exhibit clustering with either the HER2 or apocrine subtypes.<sup>9</sup>

Moreover, ILC exhibited notably reduced levels of p53 and Ki-67 expression, as well as infrequent occurrences of c-myc amplifications in comparison to luminal IDC. These findings suggest that ILC may possess an indolent characteristic, even when compared with the luminal-A subtype of IDC.<sup>9,11</sup>

In our research, it was shown that individuals diagnosed with ILC exhibited a more favorable 5-year DFS rate in comparison to those diagnosed with IDC. However, studies with extended periods of follow-up tend to indicate a comparable or potentially inferior prognosis for ILC when compared with IDC.

In the IBCSG studies by Pestalozzi and colleagues, the researchers have discovered that individuals with ILC experienced notable advantages in terms of 5-year DFS and overall survival compared with patients with IDC. However, as the follow-up period extended, these advantages diminished and were instead observed in favor of IDC patients.<sup>2</sup>

It is important to acknowledge the several limitations inherent in our study that warrants careful consideration. This study is retrospective in nature, resulting in missing data for several evaluated parameters, specifically HER2 expression. Prior to the year 2005, routine testing for HER2 expression was not conducted at our center.<sup>11</sup>

#### 4.1. Conclusion

The findings of our investigation demonstrate the therapeutic significance of categorizing invasive breast tumors into various histological subgroups. Our study demonstrated a significant correlation between lobular histology and favorable prognostic biological characteristics. However, irrespective of this, lobular histology itself is linked to improved DFS after five years and exhibits a distinct pattern of recurrence, particularly in the immediate term. The distinctions among ILC and IDC have the potential to offer valuable therapeutic resources for making more personalized treatment choices in individuals diagnosed with early-stage breast cancer.

#### Conflicts of interest

There are no conflicts of interest.

#### References

1. Elwahsh AER, Attia SG, Mahmoud MO. Evaluation of conservative breast surgery after neoadjuvant chemotherapy in breast cancer. *AIMJ*. 2022;3:54–59.
2. Pestalozzi B, 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.
3. 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.
4. Michael M, Garzoli E, Reiner CS. Mammography, sonography and MRI for detection and characterization of invasive lobular carcinoma of the breast. *Breast Dis*. 2009;30:21–30.
5. Petrelli F, Barni S. Response to neoadjuvant chemotherapy in ductal compared to lobular carcinoma of the breast: a meta-analysis of published trials including 1,764 lobular breast cancer. *Breast Cancer Res Treat*. 2013;142:227–235.
6. Abdelmabood AA, Ramadan M, Gaber AA, et al. Clinicopathological features of breast carcinoma in elderly Egyptian patients: a comparison with the non-elderly using population-based data. *J Egypt Natl Cancer Inst*. 2013;25:5–11.
7. Liedtke C, Kolberg HC. Systemic therapy of advanced/metastatic breast cancer-current evidence and future concepts. *Breast Care*. 2016;11:275–281.
8. Richter H, Hennigs A, Schaeffgen B, et al. Is breast surgery necessary for breast carcinoma in complete remission following neoadjuvant chemo-therapy? *Geburtshilfe Frauenheilkd*. 2018;78:48–53.
9. Kristiansen G, Pilarsky C. Molecular pathology of invasive lobular breast carcinoma. *Breast Dis*. 2008;30:9–14.
10. Salem MAE, Hamza HA, Abd El-Aziz NM. Neoadjuvant chemotherapy and surgical options for locally-advanced breast cancer: a single institution experience. *Middle East J Cancer*. 2017;8:127–134.
11. Smith I, Robertson J, Kilburn L, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an openlabel, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol*. 2020;21:1443–1454.
12. Link AR, Gammon MD, Jacobson JS, et al. Use of self-care and practitioner-based forms of complementary and alternative medicine before and after a diagnosis of breast cancer. *Evid Based Complement Alternat Med*. 2013;2013:301549.
13. Thomssen C, Balic M, Harbeck N, et al. St. Gallen/Vienna 2021: a brief summary of the consensus discussion on customizing therapies for women with early breast cancer. *Breast Care*. 2021;16:135–143.
14. Jung S, Jeong J, Shin SH, et al. The invasive lobular carcinoma as a prototype luminal A breast cancer: a retrospective cohort study. *BMC Cancer*. 2010;10:664.
15. Gray RG, Rea D, Handley K, et al. A TTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. *J Clin Oncol*. 2013;31(Suppl):5.
16. Biglia N, Mariani L, Sgro L, et al. 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.
17. Lee JH, Park S, Park HS, et al. Clinicopathological features of infiltrating lobular carcinomas comparing with infiltrating ductal carcinomas: a case control study. *World J Surg Oncol*. 2010;8:34.