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Now is the time to put ILC in the front!

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1. Abstract

1.1. Background: Invasive lobular Carcinoma (ILC) is distinguished from Invasive Ductal Carcinoma (IDC) via negative E-cadherin staining. Accumulating data reveal different biological and clinical behavior of ILC in both early and metastatic breast cancer. Thus, IDC usually present as a solid mass while ILC tend to present as non-mass enhancement. Clinically, ILC tends to spread to the ovaries, peritoneum and meninges and is more resistant to chemotherapy.

Current international guidelines do not consider ILC separately and do not issue distinct recommendations for this entity.

1.2. In this work we compare the treatment approach to ILC and IDC in pre and postmenopausal patients

1.3. Methods: A structured questionnaire was distributed to all breast cancer Oncologists in Israel. Two identical clinical cases were presented, the only difference being ILC or IDC histology.

1.4. Results: about 80% (n=40) of breast cancer treating oncologists in Israel answered the questionnaire, different approach were noted between IDC and ILC in identical cases. For premenopausal patients with IDC stage II (T2N1MO) Luminal B, 61.0% of the oncologists recommended neoadjuvant chemotherapy (NACT) and 22% opted to upfront surgery, while for ILC only 26.8% initiated NACT and 39.0% chose upfront surgery. The difference was statistically significant (P=0.014). In postmenopausal patients, there was numerically but not statistically significant difference between the treatment approaches.

1.5. Conclusions: although international guidelines do not consider ductal and lobular histology separately, oncologists' treatment approach differs between premenopausal patients with IDC versus ILC histology.

2. Introduction

Invasive lobular Carcinoma (ILC) is the second most common type of breast cancer, after Invasive Ductal Carcinoma (IDC), and accounts for 10-15% of all cases.

The key molecular hallmark of ILC is the loss of E-cadherin protein encoded by CDH1 gene[16]

The incidence of breast cancer increases with age so given the

prolongation of life expectancy more patients will be diagnosed with breast cancer in coming years. The incidence of ILC subtype also increases over the years, mainly among post-menopausal women [13] and those who used hormone replacement therapy [19]

ILC is predominantly estrogen receptor and progesterone receptor positive [21]. In the past, ILC was perceived a favorable subtype and its diagnosis did not play a major role in therapeutic decisions. With time, it evolved as a distinct entity with clinical, biological and prognostic differences [14].

Unlike IDC that usually form a detectable mass, in ILC, the loss of E-cadherin, a trans-membrane glycoprotein that play a key role in cell-cell adhesion, leads to a linear growth pattern [16] and is less likely to form a mass [20], making it harder to diagnose both clinically and radiologically.

Consequently, ILCs are poorly visible on mammography leading to false negative rate of up to 30%[28] and resulting in delayed diagnosis at more advanced stages. [16, 29]

Moreover, systemic staging is also a challenge, as ILC is less FDG-avid [24], and involved lymph nodes or metastasis can be missed, leading to stage misclassification and potentially inadequate treatment.

Several studies indicate that ILC is more resistant to chemotherapy compared to IDC[2, 5]. A retrospective study of patients with stage I/II IDC or ILC concluded that unlike IDC, adjuvant chemotherapy did not improve overall survival (OS) for patients with ILC[7]. This finding was supported by a population-based study from the Netherlands Cancer Registry, where adjuvant chemotherapy was associated with improved 10-year survival rates for postmenopausal patients with IDC, but not for those with ILC[8]. Another study concluded that disease-free and overall survival were worse in patients with ER positive ILC than in patients with ER-positive IDC [16].

Pestalozzi et al examined the DFS and OS after adjusting for the baseline factors as chemotherapy treatment, after 6 years, the risk of a DFS event was 54% higher for the ILC cohort compared with the IDC cohort and the risk of a death was 50% higher for the ILC cohort for OS after 10 years, compared with the IDC cohort [14]. Furthermore, a study of patients with ILC and involved axillary nodes demonstrated that NACT resulted in lower rates of pathological complete response (pCR), and did not reduce the rate of mastectomies or the extension of axillary surgery, when compared with IDC. Moreover, for ILC the OS was worse with NACT as compared to adjuvant therapy[4].

Regardless of these differences between IDC and ILC, the international guidelines do not classify these entities separately. In our questionnaire-based study, we aim to assess if the Israeli oncologists approach IDC and ILC differently in daily practice.

3. Methods

The study was reviewed and approved by the institution's research ethics committee.

A structured questionnaire was developed and distributed to all breast cancer Oncologists in Israel. Two identical theoretical patients with stage II, Node positive, HR+ positive, Her2-

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negative cases were presented, the only difference being histology of IDC or ILC. The questions were repeated twice- for Pre and postmenopausal patients. The first part of the questionnaire focused on the medical expertise levels, workload, and geographical parameters. None of the questions was mandatory. In the second part, the oncologist's management of the case was assessed.

The questionnaire was disseminated via the digital platform WhatsApp and allowed for anonymous responses. All replying physicians agree to participate in the study.

The study was conducted over a one-month period in July 2023.

4. Population

The questionnaire was distributed to all Oncologists specializing in breast cancer across Israel.

5. Statistical Analysis

The association between categorical variables was assessed using either the Chi-square or the Fisher's exact tests. All statistical tests applied were two-tailed, and a p-value of $\leq 0.05\%$ was considered as significant.

6. Results

In Israel, there are approximately 60 medical oncologists treating breast cancer. About one third are key opinion leaders specializing in breast cancer treatment, one third exclusively focused on breast cancer treatment, and the rest practice general oncology and treat breast cancer as well as other malignancies.

The surveyed oncologists included all those actively engaged in the treatment of breast cancer. We received responses from 40 out of 60 oncologists (66%), and all questionnaires were answered completely. Answers were received from 85% of tier 1, 65% of tier 2 and 10% of tier 3. Regarding the geographical distribution, 65% of the physicians surveyed are practicing in the central region, 20% in the south, and 15% in the northern regions of Israel.

A summary of the demographics of the participating medical oncologists is shown in Table 1.

Table 1 Demographics of participating medical oncologists

Years of practice (median)		
	resident	2 (5%)
	4 Jan	7 (17.5%)
	9 May	17 (42.5%)
	20 Oct	14 (35%)
Location of practice	Center	26 (65%)
	South	8 (20%)
	North	6 (15%)
Number of breast oncologists in the center	One	4(10%)
	More than 1	36 (90%)
Number of patients per month		
	19 Jan	7 (17.5%)

	20-49	12 (30%)
	50-100	9 (22.5%)
	>100	12 (30%)

In the questionnaire, we presented two identical clinical cases, differing only in histology, one being IDC and the other ILC. This was done to assess variations in treatment approaches between these two subtypes.

In the first case, a premenopausal patient with IDC stage IIB (T2N1M0) Luminal B subtype was introduced. We queried physicians about their initial decision, revealing that the majority, 61.0%, would opt for initiating neoadjuvant chemotherapy (NAC) if the histology was IDC. However, only 26.8% would do the same if the histology was ILC. Table 2 provides a summary of responses to this question.

Further distinctions emerged in the responses: 22.0% would recommend upfront surgery for the patient with IDC, contrasting with 39.0% for ILC. Additionally, 17.1% would suggest molecular testing as part of the decision-making process for IDC, while 34.1% would do so for ILC. Notably, the disparity in the initial decision was statistically significant ($P=0.014$).

The subsequent question pertained to scenarios where the patient underwent upfront surgery and the pathology results indicated stage IIB disease (T2N1MO), revealing that the majority of oncologists would recommend molecular testing for both subtypes (63.4% for IDC versus 70.7% for ILC). In cases of IDC, 36.6% would promptly initiate chemotherapy treatment, compared to 22.0% for ILC. Notably, none of the oncologists would opt solely for adjuvant endocrine therapy in IDC, whereas 7.3% would do so in ILC ($P=0.097$).

The final question addressed the decision-making process when six out of ten lymph nodes were involved. Here, the majority of physicians (95.1% for IDC and 92.7% for ILC) would initiate chemotherapy treatment, and no statistical difference was observed ($P=1$).

In the second case, we presented a postmenopausal patient with the same clinical stage, IIB, Luminal B subtype. Again, we sought input on the initial decision. In contrast to the premenopausal patient with IDC (61% opting for NAC), only 2.4% would choose NAC for both IDC and ILC cases in postmenopausal patients. NA endocrine treatment was recommended to 4.9% for IDC versus 12.2% for ILC.

Overall, the neoadjuvant (NA) option, whether endocrine or chemotherapy, was not favored. For IDC, 39% of patients would be directed to upfront surgery compared to 56.1% for ILC. Molecular testing support was more prevalent for IDC (53.7%) than for ILC (29.3%). If pathology post-surgery indicated stage IIB, more than 90% would recommend molecular testing, with no statistical difference between the two histological types. Similarly, in cases where six lymph nodes were involved instead of two out of ten, the vast majority would initiate adjuvant chemotherapy, with only 4.9% versus 14.6% settling for endocrine treatment alone.

Table 2 Answers/Responses

Question regarding treatment approach in premenopausal patient A 43 year old female, healthy, premenopausal, with no family

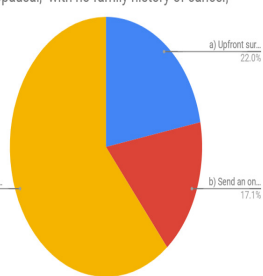
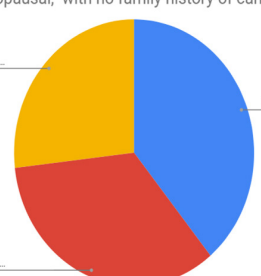
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history of cancer, palpated a breast lump. Mammography demonstrated a 2.5 cm right-sided breast mass and sonography a pathologic lymph node with thickened cortex. Breast biopsy showed infiltrating carcinoma ER+3 PR+ 1HER2-0 KI67 20%, and the lymph node was involved by carcinoma. No additional lesions on MRI. CTPET showed one breast mass ~3 cm and 3 axillary lymph nodes, no distant metastasis, physical examination correlates to imaging

it is perceived as a very high risk for recurrence.

Differences in treating postmenopausal versus premenopausal woman was noticed,

For example, only 2.4% would give NACT for both IDC and ILC cases rather than 61% for premenopausal with IDC. Still in postmenopausal woman there were no statistical differences between the subtypes. Emphasizing the confusion is more pronounced in younger woman.

What will you recommend if it was IDC?		What will you recommend if it was ILC		
a. Upfront surgery	9 (22.0%)	Count of A 43 year old female, healthy, premenopausal, with no family history of cancer, 	16 (39.0%)	Count of 1. A 43 year old female, healthy, premenopausal, with no family history of cancer, 
b. Send for molecular testing	7 (17.1%)		14 (34.1%)	
c. Initiate chemotherapy	NA 25 (61.0%)		11 (26.8%)	

7. Discussion

Israel is among the counties with the highest incidence of breast cancer in the world [11], according to the WHO report (Globocan 2020) it is situated in the 26th place. This is partially attributed to high prevalence of mutations in the high-risk genes BRCA1 and BRCA2 among women of Ashkenazi Jewish heritage [12].

Analyzing the data from our study revealed the difference in confidence level of oncologists while treating IDC versus ILC.

In the first case we presented premenopausal patient with IDC stage II, it appears that the majority of the oncologists 61.0% were confident to initiate NACT as oppose to 26.8% in ILC which was significant statistically. The main purpose of NACT is to decrease the extent of surgery, in breast or in axilla. Still prospectively randomized neoadjuvant trials revealed mastectomy rate was higher in ILC compared with non-ILC patients irrespective of response to NACT. Therefore it was not surprising almost double will send to upfront surgery (39.0% Vs 22.0%).

Double the amount of oncologist sending molecular testing to aid decision in ILC versus IDC (34.1% Vs 17.1%) though in the present the predictive value of molecular testing in ILC is inconclusive.

Studies using Oncotype 21-gene assay demonstrated that adjuvant chemotherapy was associated with improved overall survival (OS) in IDC but not in ILC. Similar results were observed in another trial, where ILC was associated with statistically significantly worse disease-free survival and overall survival compared to ER-positive IDC, although 6 times more IDCs were classified as high risk by Oncotype Dx Breast Recurrence Score assay. Likewise, a statistically significant association between RS and outcome was noted in IDC but not in ILC [16].

Having six or more lymph node involved led the oncologist to treat with chemotherapy no matter the subtype, probably because

This reflects the differences in perception between IDC and ILC which eventually leads to a change in treating decisions. The inferior prognosis of ILC patients implies that using the same treatment recommendations as for IDC is not in favor of ILC patients. It is also emphasizing the need to encourage vast research in ILC that will enable in the future more precise guidelines recommendations for each subtype.

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