

A review of invasive lobular carcinoma of the breast: Should it be treated like invasive ductal carcinoma?

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Abstract

In this article, we review the evidence detailing the clinical, pathological and genomic differences between invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC) of the breast. Even within ILC, there is great variation within its subtypes. Although current guidelines suggest that ILC and IDC should be managed similarly, future trials should stratify by histological subtype and more research needs to be done to elucidate molecular characteristics, so as to better tailor and optimise treatment for patients.

Introduction

There is increasing evidence that invasive lobular carcinoma (ILC) differs from invasive ductal carcinoma (IDC), in their clinical, pathological and genomic characteristics, yet current guidelines suggest that they be managed similarly, against many physician's opinions [1]. Even within ILC, there is great variation within different histological subtypes. We aim to provide a concise review of the peculiarities of breast ILC.

Epidemiology and pathogenesis

ILC is the second most common breast cancer subtype [2] accounting for about 10% of breast cancer cases. Even within ILC, there are more than ten histopathologic variants [3], including the classical subtype (56%), the alveolar variant (15%), the solid subtype (11%), the mixed non-classic variant and the pleomorphic variant. Most ILC are hormone receptor- positive and HER2 receptor negative [4], with up to 95% being estrogen receptor (ER) positive, and 70% being progesterone receptor (PR) positive. They most often belong to the luminal molecular subtype [5] with most not expressing HER2 nor basal epithelial markers. The pleomorphic variant of ILC however shows a relatively higher frequency of HER2 expression of up to 35 - 80% and is more often ER-negative or triple negative [6], with only 10 - 76% of pleomorphic ILC being ER-positive. Correspondingly, the proliferation index is typically higher and the tumour displays a more aggressive clinical course [7,8].

Since ILC is commonly strongly ER- and PR- positive, it is expected that traditional hormone-related risk factors causing increased estrogen exposure will also be applicable. Several observational studies suggest that the relative risk of breast cancer for a post-menopausal woman on combined hormonal replacement therapy was higher for that of ILC than for IDC [9,10], with the relative risk of 1.5 for IDC compared to more than 2.0 for ILC [11]. There was less of such a differential risk by histological subtype for the use of estrogen hormonal therapy however, with a relative risk of 1.1 for IDC and 1.4 for ILC. Similar findings were reported for other traditional hormone-related risk factors such as early menarche, later age of menopause [12] and later age at first birth [13,14], with stronger associations shown between the risk factor for ILC than for IDC. To the best of our knowledge, there is no current

published data on the different risk of oral contraceptives on different histological subtypes of breast cancer [11]. Among other lifestyle factors, alcohol consumption of seven or more alcoholic beverages also conferred a higher risk for ILC than for IDC among post-menopausal women [15,16].

Of the four high penetrance genes with known genetic susceptibility to breast cancer, *BRCA1* and *TP53* are predominantly associated with IDC, *BRCA2* mutations are associated with both ductal and lobular subtypes while *CDH1* mutations are exclusively associated with ILC breast cancers [11]. The frequency of ILC breast cancers in *BRCA2* mutation carriers is around 8.4%, similar to that in the general population, while ILC is grossly underrepresented in proportion among *BRCA1* mutation carriers [17].

Familial clustering of ILC has also been reported. Some of these cases are associated with germline mutations in the *CDH1* gene on chromosome 16q. The *CDH1* gene codes for the E-cadherin protein, which plays a role in cell adhesion [18]. Germline inactivation in this tumour suppressor gene has also been associated with diffuse gastric cancer (DGC). Loss of E-cadherin is thought to be oncogenic both loss of cellular cohesion, as well as by triggering secondary changes such as the loss of beta-catenin and aberrant cellular location of p120-catenin; leading to promotion of cancer cell motility, migration and invasion [19,20]. Even in the absence of inherited germline mutations in *CDH1*, the loss of E-cadherin expression is almost a universal occurrence in ILC [21,22], largely due to somatic *CDH1* frameshift mutations and loss of heterozygosity or aberrant *CDH1* promoter methylation [23]. On the contrary, E-cadherin expression is almost always intact in IDC [24]. Other genetic abnormalities commonly implicated include mutations of the *PIK3CA/AKT/PTEN* [25] and *FOXA1* genes [26] and *ESR1* copy number gains [27], while mutations of *TP53* and *GATA3* are rare unlike in IDC, with the exception of the pleomorphic variant of ILC.

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Imaging

The mammographic detection of ILC is more difficult than that of IDC due to its diffuse infiltrative pattern of growth with indistinct margins, causing mammography to be less sensitive for its detection [28]. Rather than a discrete well-circumscribed mass with a central opacity, the typical mammographic finding for ILC is a spiculated, poorly-defined mass with asymmetrical densities [29] or simply, architectural distortion. Calcifications are also a rarely seen mammographic finding in ILC [30]. Sensitivity of mammogram for ILC hence is reported to be around 57 – 81% [29], lower than that for IDC, with up to a third of ILC tumours being missed [31].

As such, other modes of imaging are frequently used to complement that of mammography, with both ultrasound [32] and magnetic resonance imaging (MRI) [33] showing higher sensitivities for ILC detection. On ultrasound, similar to mammography, ILC is rarely seen as a well-circumscribed mass and even up to 20% of cases may lack typical sonographic features of posterior acoustic shadowing. More than 10% of ILC may be undetected with ultrasound, with a sensitivity of 68 – 98% [32,34,35], higher than that of mammography, even when taking into account that some of these studies used older sonographic techniques. More importantly, 73% of ILC tumours that could not be detected by mammography could be identified by ultrasound and 92% of ILC tumours with only subtle findings on mammography were confirmed by ultrasound [32]; reinforcing the usefulness of sonography as an adjunct to mammography in ILC diagnosis.

Breast MRI has a higher sensitivity of 93% for detection of ILC but also comes at a tradeoff of reduced specificity [33].

In addition to its use as screening in women with a high lifetime risk of breast cancer [36], MRI has also been studied in a role for preoperative imaging and planning. In the latter, though routine use is still controversial, in some studies it has been shown to influence surgical management in about a quarter of cases when used for preoperative planning [37], with lower rates of re-excision with better definition of disease extent upfront.

Promising techniques such as breast specific gamma imaging (BSGI) [38] and tomosynthesis [39,40] are currently being studied as imaging adjuncts to conventional methods for ILC. BSGI, or molecular breast imaging (BMI) has the highest sensitivity among all the imaging modalities for breast cancer, and also for ILC, at 93%. It however requires exposure to higher radiation doses, but still is a promising adjunct modality [38]. Breast tomosynthesis is a low-dose mammogram technique with greater ability in detecting architectural distortion [40], a common imaging feature of ILC. When combined with digital mammography, it has been shown to increase the detection rate of ILC compared to the latter modality alone [39].

Treatment and prognosis

Although breast conservation surgery (BCS) is a viable option for ILC [41], there is an increased incidence of positive resection margins as compared to patients who underwent BCS for IDC [42], resulting in a need for a second operation to ensure complete excision. Mastectomy is more often performed in ILC with one series reporting mastectomy rates of 57% in ILC patients compared to 46% in IDC [43]. This may be due to the larger size of ILC tumours as well as their multifocality.

The response rates of ILC tumours to neoadjuvant chemotherapy are lower than that of IDC with 41% of ILCs being downstaged compared to similar downstaging in 64% of IDCs in one series [44].

In the same series, pathological complete response (pCR) rates were also lower in ILC at 3.5% compared to IDC at 14%, though histological subtype alone was not a statistically significant factor [44], and instead, this has been postulated to be related to their low grade and proliferative rates [45]. The magnitude of benefit from trastuzumab however is similar for both ILC and IDC [46].

Even though ILC responds poorly to neoadjuvant chemotherapy, it has been shown to respond well to endocrine therapy [47]. However, the magnitude of benefit differs with different endocrine therapy. There is also preclinical data that tamoxifen is not an ideal endocrine therapy in ILC patients, with ILC tumour models showing a paradoxical induction of cellular proliferation in response to the drug, suggesting that the estrogen receptor may have different isoforms [48,49], or drive different signaling pathways in the two histological subtypes [50,51]. Differential ER activity between the IDC and ILC has also been suggested at a gene expression level [26]. Clinically, this has also been observed in several retrospective analyses showing that post-menopausal patients with ILC derive more a greater magnitude of benefit from aromatase inhibitors than do patients with IDC [52,53]. Analysis of patients in the Breast International Group (BIG) 1-98 trial showed that letrozole was associated with a 50 – 66% reduction in DFS event risk in ILC patients compared to a 0 – 35% risk reduction in patients with IDC [52]. This difference may however possibly be ameliorated by a switch from tamoxifen to an aromatase inhibitor [54].

Although short term disease free survival is often better in ILC [55], higher rates of late recurrences have been documented and long-term overall survival rates do not differ significantly between the two subtypes [56,57] or may even be worse for ILC [58]. Up to 30% of patients developing subsequent metastatic disease [59]. The pattern of metastases from ILC also shows an interesting distribution, with more gastrointestinal [60] and peritoneal or ovarian metastases [61], and less lung metastases compared to their IDC counterparts [60]. Gastric metastases seem to be particularly common, and should be differentiated from a primary gastric tumour [62], especially in view that both ILC and diffuse gastric cancers can occur together in the hereditary diffuse gastric cancer (HDGC) syndrome [63].

Conclusion

ILC differs greatly from IDC in many important ways. From sensitivity of imaging techniques in their detection, to pathological and molecular characteristics, these two subtypes have significant differences that contribute to their different clinical course, responses to treatment and prognosis. Even within ILC, there is great heterogeneity. Current guideline recommendations that both histological subtypes should be managed similarly stems more from insufficient knowledge and data rather than a true belief that the two subtypes should be managed identically.

Future trials should stratify recruitment by histological subtype and more studies are needed to evaluate the molecular characteristics of ILC. This will allow us to better understand the disease biology of ILC better and help us better tailor treatment choices for patients.

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