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Invasive lobular carcinoma of the breast: Response to hormonal therapy and outcomes ☆

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ABSTRACT

Invasive lobular carcinoma (ILC) comprises approximately 5–15% of breast cancers and appears to have a distinct biology. It is less common than invasive ductal carcinoma (IDC) and few large studies have addressed its biologic characteristics and behaviour with respect to long-term clinical outcome and response to adjuvant therapy.

Methods: This study is based on a large and well-characterised consecutive series of invasive breast carcinomas with a long-term follow-up (up to 25 years). This series included 415 (8%) patients with pure ILC and 2901 (55.7%) with IDC (not otherwise specified) identified from a consecutive cohort of 5680 breast tumours presented to our Breast Unit that were treated in a similar conventional manner. Clinicopathological, therapy and outcome information as well as data on a large panel of biomarkers were available.

Results: Compared to IDC, patients with ILC tended to be older and present with tumours which are more frequently lower grade (typically, grade 2 [84%]), hormone-receptor positive (86% compared to 61% in IDC), of larger size, and with the absence of vascular invasion. A higher frequency of ILC was placed in the good Nottingham Prognostic Index group (40% compared to 21% in IDC). ILC showed indolent but progressive behavioural characteristics with nearly linear survival curves which crossed those of IDC after approximately 10 years of follow-up, thus eventually exhibiting a worse long-term outcome. Importantly, ILC showed a better response to adjuvant hormonal therapy (HT) with improvement in survival in patients who received HT compared with matched patients with IDC.

Conclusion: ILC is a distinct entity of breast cancer that responds well to adjuvant HT. These data add important clinical information for assessing the long-term benefits of adjuvant HT use in ILC.

☆ This study was approved by Nottingham Research Ethics Committee 2 under the title of 'Development of a molecular genetic classification of breast cancer'.

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1. Introduction

Breast cancer represents a heterogeneous group of tumours with varied behaviour, and response to therapy. Invasive lobular carcinoma (ILC) is the commonest special type of breast cancer and the second most common overall type of breast cancer, accounting for 5–15% of cases.[1,2] Whereas the incidence of invasive duct carcinoma of no special type (IDC) has remained stable, the incidence of ILC appears to be increasing especially amongst postmenopausal women[3] and maybe related to the use of HRT.[4]

Several studies have shown that ILC is a distinct entity of breast cancer that differs from IDC not only in histological and clinical features but also in risk factors,[1,2,5] global transcription programmes[6] and genomic profiles.[7] ILC is frequently associated with older age, larger tumour size, lower histologic grade and positive hormone receptors (HR).[1,8–10] It has been described as having a higher rate of multiple metastases,[11] with a distinct pattern of involvement of distant sites.[12–14] Some long-term follow-up studies have shown a trend to later locoregional recurrence.[15,16] However, as ILC is substantially less common than IDC, knowledge about the clinical outcome of ILC has been based on studies including relatively small numbers of patients and most of the available reports do not have comprehensive data for long-term follow-up. Reported prognosis varies and has been reported to be worse,[17,18] no different[14,19–23] or better[9,24–28] than that with IDC.

In addition, it has been reported that ILC is less responsive to chemotherapy,[8,16,25,29] lacks potential benefit of HER2-targeted therapy,[1,30,31] being typically HER2 negative, but is more often HR positive and responsive to adjuvant hormonal therapy (HT).[8,26] Therefore, patients with ILC are regarded as good candidates for adjuvant endocrine therapy to improve overall survival. However, some previous studies had documented that ILC patients received less adjuvant treatment.[21] The effect of HT on the long-term outcome of ILC patients had not been previously studied.

Therefore, in this study, we performed a retrospective analysis of a large and well-characterised series of breast cancers with long-term follow-up comprising clinicopathologic and outcome information; data on a wide range of proteins of known relevance in breast cancer were also available. Our aim was to perform a comprehensive comparison of ILC and IDC and provide a more complete and reliable assessment of the biologic phenotype, clinical behaviour of ILC and to assess its long-term outcome particularly in relation to the use of adjuvant HT to support clinical decision making.

2. Materials and methods

The study population was derived from the Nottingham Tenovus Primary Breast Carcinoma Series from women aged 70 years or less who presented with primary operable invasive breast carcinomas between 1974 and 2004. This is a well-characterised series of patients with a long-term follow-up that has been treated in a single institution. All patients received standard surgical treatment of either mastectomy or wide local excision with radiotherapy. Prior to 1988 no patients received adjuvant hormonal therapy (HT) or chemotherapy, after 1988 adjuvant treatment was managed on the basis of patients' tumour prognostic and predictive factor status. Treatment was based on Nottingham Prognostic Index (NPI) score derived from grade, size and lymph node (LN) stage.[32] Patients in the good prognostic group were not offered adjuvant therapy. HT was offered to patients with oestrogen receptor (ER) positive tumours and NPI scores of >3.4 (moderate and poor prognostic groups). Premenopausal patients in the moderate and poor prognostic groups were offered CMF chemotherapy and those oestrogen receptor (ER) positive, LN positive patients were offered CMF and HT. Postmenopausal patients in the moderate and poor prognostic groups were offered HT if ER positive and if ER negative, the option of CMF if fit. Assessment of progesterone (PgR) was not carried out routinely and was not used in clinical decision making. This was commonplace in the UK at that time.

Patient's clinical history and tumour characteristics including referral type, patients' age, menopausal status, bilaterality, family history, type and number of primary operation and axillary LN surgery, primary tumour size, histologic tumour type, histologic grade, degree of tubule formation, nuclear pleomorphism and mitosis, LN status, vascular invasion (VI) and NPI and ER status were obtained from the database. Survival data including survival time, disease-free interval and development of distant metastasis (DM), local and regional recurrence was maintained on a prospective basis. Patients were followed up at 3-month intervals initially, then 6-monthly and annually for a median period of 76 (range 1–369 months). Breast cancer specific survival (BCSS) was defined as the interval between the operation and death from breast cancer, death being scored as an event, and patients who died from other causes or were still alive were censored at the time of last follow-up. Disease-free interval (DFI) was also calculated from the date of first operation, with first recurrences, local, regional or distant, being scored as an event and with censoring of other patients at the time of last follow-up or death. Local recurrence was defined as tumour arising in the treated breast or chest wall. Regional recurrence was defined as tumour arising in the axillary or internal mammary LNs.

In addition, data on several other prognostic biomarkers with close relevance to breast cancer were available on 1315 cases (1095 IDC and 220 ILC). These markers included PgR and androgen (AR) receptors, EGFR, HER2, c-erbB3, c-erbB4, p53, P-cadherin, E-cadherin, FHIT protein, bcl2, p21, TGF-A, neuroendocrine markers (chromogranin-A and synaptophysin), MUC-1, SMA, p63 and basal (CK5/6 and CK14) and luminal cytokeratins (CK7/8 and CK19).[33,34]

3. Statistical analysis

Statistical analysis was performed using SPSS 13.0 statistical software (SPSS Inc., Chicago, IL, USA). The clinical and biologic characteristics of ILC and IDC were compared using contingency tables, χ^2 tests, Fisher's exact tests and Student's *t*-tests. BCSS and DFI curves were drawn using Kaplan–Meier