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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

estimates, and were compared using log rank tests and the Generalised Wilcoxon test 'Breslow test'. Survival rates are presented with their 95% confidence intervals. Multivariate analyses of DFS and BCSS, with stepwise variable selection, were conducted using Cox proportional hazard regression models. A p-value <0.05 was considered significant. Cut-off values for the different IHC biomarkers included in this study were chosen before statistical analysis. Standard cut-offs were used for established prognostic factors and were the same as for previously published data.[33,34]

4. Results

From the 5680 breast tumours, 415 (8%) invasive lobular carcinomas (ILCs) and 2901 (55.7%) invasive ductal carcinoma of no special type (duct/NST, IDC)[35] were identified. Cases of mixed tumour types including mixed ILC and IDC and mixed duct/NST and special types were identified, however, those mixed cases similar to special histologic types such as tubular, tubular mixed, mucinous and medullary-like, and those with locally advanced or with DM at diagnosis were not included in the analysis; only pure IDC and pure ILC were considered in this study. ILC was not further subtyped in this series. Hormonal therapy (HT) was given to 1104 patients (37.7%) and chemotherapy to 655 patients (22.5%). Of those patients who received HT, 85% received tamoxifen and 10% were given tamoxifen and zoladex while the remaining 5% received other types of endocrine therapy such as high dose progesterone, ovarian ablation or an aromatase inhibitor. One hundred and thirty nine patients with ILC (37%) received adjuvant HT while only 23 patients (6.2%) received chemotherapy (CT).

Table 1A – Association between tumour type (ILC and IDC) and clinicopathological features

Variables	ILC No. (%)	IDC No. (%)	p-value
Patients' age (<50 years)	102 (24.6)	1059 (36.5)	**<0.001**
Menopausal status[a]	300 (72.5)	1809 (62.5)	<0.001
Method of referral[b]	316 (77)	2273 (79)	0.41
Positive family history	100 (24)	680 (23.5)	0.76
Bilaterality	22 (5)	94 (3.2)	0.13
Type of operation[c]	143 (35)	1073 (37)	0.33
Axillary LN[d]	67 (19.2)	627 (25.1)	**0.039**
Size			
<2 cm	230 (55)	1713 (59)	**<0.0001**
2–5 cm	157 (38)	1135 (39)	
>5 cm	28 (7)	51 (2)	
Grade			
1	28 (6.7)	135 (4.7)	**<0.0001**
2	346 (83.4)	943 (32.5)	
3	41 (9.9)	1823 (62.8)	
LN stage			
1	252 (60.7)	1771 (61)	0.11
2	104 (25)	811 (28)	
3	59 (14.3)	319 (11)	
NPI			
Good	166 (40)	628 (22)	**<0.0001**
Moderate	198 (47.7)	1683 (58)	
Poor	51 (12.3)	590 (20)	
Definite VI	56 (16.8)	819 (35.5)	**<0.001**
Hormonal treatment	139 (37)	965 (38)	0.88
Chemotherapy	19 (5)	574 (23.3)	**<0.001**
Development of recurrence	142 (35.2)	991 (35.1)	0.88
Distant metastasis	113 (28)	769 (27.2)	0.65
No. of BC deaths	124 (29.9)	825 (28.4)	0.305

LN, lymph node (1 = negative; 2 = 1–3 positive nodes, 3 = 4 or more positive nodes), NPI, Nottingham Prognostic Index.
a Number of postmenopausal women (as compared to premenopausal women).
b Number of symptomatic patients (as compared to screening women).
c Wide local excision (as compared to mastectomy).
d number of patients with axillary lymph node clearance (as compared to axillary node sample).

Tables 1A and 1B summarise the clinicopathologic and immunophenotypic features of ILC as compared to IDC. The mean age of patients with ILC was 3 years older than that of patients with IDC (57 and 54 years, respectively) and more likely to be postmenopausal. ILC were slightly larger on average with a greater chance of ILC presenting as a larger tumour. Despite the larger tumour size, ILC showed more favourable biologic characteristics. The majority were of lower histologic grade (grade 2 tumours) and were associated with less vascular invasion. Compared to IDCs, ILCs were much more likely to express hormone receptors (ER, PgR and androgen receptors), to be negative for biomarkers associated with poor prognosis in breast cancer (p53, P-cadherin, basal CKs, EGFR, HER2 and cerbB4) and to have normal BRCA1 and MUC1 expression (Table 1). Absent or reduced E-cadherin expression (H-score <100) was detected in 81% of ILC compared to 32% in IDC (($\chi^2 = 379$, $p < 0.0001$). No difference was identified between ILC and IDC regarding other biomarkers included in this study. Despite the higher hormone receptor content in ILC, the proportion of patients who received adjuvant endocrine therapy was not different between ILC and IDC. The number of patients with ILC who received adjuvant chemotherapy was significantly lower than in IDC (Table 1).

The pattern of metastatic dissemination between the two tumour types was also different (Table 2). ILC was three times less likely to metastasise to lung and two times less to liver and brain ($p < 0.001$). Metastasis to bone was more frequently observed in ILC than IDC ($p < 0.001$). No difference was detected in the case of metastasis to pleura or metastasis to multiple sites. The detail of coding in the database was not sufficient to permit further distinction of other metastatic sites (e.g. peritoneum, gastrointestinal tract and ovaries), and therefore their incidence could not be determined.

5. Outcome

Analysis of BCSS and DFI showed no significant difference between ILC and IDC ($p > 0.05$). However, a trend towards better survival was observed for ILC patients during the initial years of follow-up (approximately 130 months), subsequently the two survival curves converged after that and the ILC patients show a continued decline in both DFI and BCSS in a nearly linear way while that of IDC showed

Table 1B – Association between tumour type (ILC and IDC) and different protein expression patterns

Biomarkers[a]	Cut-off values (%)	ILC (220 cases) No. (%)	IDC (1095 cases) No. (%)	*p*-value
Positive ER (whole series)	>20	307/356 (86)	1612/2643 (61)	<0.001
Positive PgR	>20	134 (68)	444 (44)	<0.001
Positive androgen	>20	172 (90)	528 (54)	<0.001
Positive p53	>5	20 (10)	381 (37.4)	<0.001
Positive P-cadherin	>5	46 (28)	544 (62)	<0.001
Positive EGFR	>10	9 (5)	218 (24)	<0.001
Positive HER2	>10	10 (4)	232 (23)	<0.001
Positive cerbB3	>10	135 (83)	790 (92)	<0.001
Positive cerbB4	>10	97 (57)	760 (88)	<0.001
Positive basal CKs	>10	15 (7)	238 (23)	<0.001
Strong luminal CKs positivity	>200[b]	175 (84)	762 (73)	0.003
Positive ME markers	>10	3 (1.5)	175 (17)	<0.001
Positive NE markers	>5	4 (2)	136 (15)	<0.001
Absent nuclear BRCA1	0	5 (3)	174 (20)	<0.001
Loss of MUC1 expression	0	7 (4)	110 (13)	<0.001

Basal CKs = CK5/6 and/or CK14, ME, myoepithelial markers (SMA and/or p63); NE, neuroendocrine; luminal CKs, CK7/8 and/or CK19.
a Immunohistochemical markers were available in 220 ILC and 1095 IDC,[33,34] except ER data which were available for the whole series.
b Histo-score (0–300; calculated as follows: intensity [1–3] × percentage of positive cells [0–100%]).

Table 2 – Metastatic patterns of ILC as compared to that of IDC

	ILC No. (%)	IDC No. (%)
Bone	52 (44)	223 (28)
Liver	13 (11)	149 (19)
Pleura	11 (9)	57 (7)
Lung	9 (8)	158 (21)
Brain	3 (3)	49 (6)
Other lymph nodes[a]	19 (16)	112 (14)
Other sites	10 (9)	35 (5)

a Other lymph nodes, e.g. intra thoracic, intra-abdominal or groin LN.

a plateau (Figs. 1A and 1B). Therefore, we repeated the analysis using Breslow's test, which is more sensitive to subtle changes in survival pattern.[36] Importantly, Breslow's test showed a significant difference in the survival between the two tumour types and gave *p*-values which are very different to the log-rank *p*-value (Breslow = 6.83, $p = 0.009$ and Breslow = 5.1, $p = 0.024$ for BCSS and DFI, respectively). Similar observations were found in the different matched subgroups (matched LN stage and NPI groups) and after adjustment for grade or LN stage. Importantly, multivariate Cox regression analysis performed after adjustment for other prognostic indicators, including LN status, tumour size, histologic grade, vascular invasion and ER status, HT, tumour type (IDC versus ILC), showed that tumour type is independently associated with survival (Hazards Ratio 1.16, 95% CI 1.01, 1.3, $p = 0.034$). In addition, to rule out the possibility that the time-varying hazards between ILC and IDC are due to different distributions of ER status, analyses were performed after stratifying the cases according to ER status and similar patterns were observed in both ER-positive and ER-negative subgroups (Figs. 1C and 1D).

To evaluate the effect of adjuvant HT on the outcome of the two tumour type groups, survival analyses were repeated according to the use of HT (cases presented between 1988 and 2004). In the group of patients who did not receive HT, the outcome showed a similar pattern to the whole series. However, we identified an improvement in the outcome of ILC patients who received HT compared to that of IDC patients (LR = 3.3, $p = 0.071$). To confirm this observation and to rule out any possible confounders, analyses were also performed using a multivariate Cox regression analysis after adjustment for other prognostic indicators, including LN status, tumour size, histologic grade, vascular invasion and ER status, HT, tumour type (IDC versus ILC) as well as an interaction term between the histologic type and HT (histologic type*HT). Multivariate analyses showed that the interaction term is statistically significant (Table 3) confirming a better response of ILC than IDC to HT. Furthermore, univariate analyses were repeated on different matched subgroups from the whole series and these results also showed a better response of ILC to HT (Figs. 2A–2D).

Survival analysis of pure ILC patients showed that LN stage is the strongest predictor of both BCSS and DFI (LR = 63.5, $p < 0.001$ and LR = 36.6, $p < 0.001$ for BCSS and DFI, respectively) followed by grade, vascular invasion, size, ER status and HT while other biomarkers included in this study were not significant. Interestingly, the association between HT and better survival of ILC patients was observed in the whole series (LR = 3.8, $p = 0.05$ and LR = 12.8, $p = 0.0004$ for BCSS and DFI, respectively) and in the different subgroups (e.g. in the LN positive subgroup, LR = 9.8, $p = 0.001$, LR = 27.9, $p < 0.001$ for BCSS and DFI, respectively). Multivariate analyses, after adjustment for other prognostic indicators, were performed to determine whether HT was an independent prognostic factor for BCSS and DFI in patients with ILC. This showed that HT is an independent predictor of survival in ILC (Hazards Ratio 0.32, 95% CI 0.17, 0.6, $p < 0.001$). These findings were found in the whole ILC series and in the different subgroups. No further analysis regarding adjuvant chemotherapy (CT) was performed since only 19 cases (5%) in this series received CT.

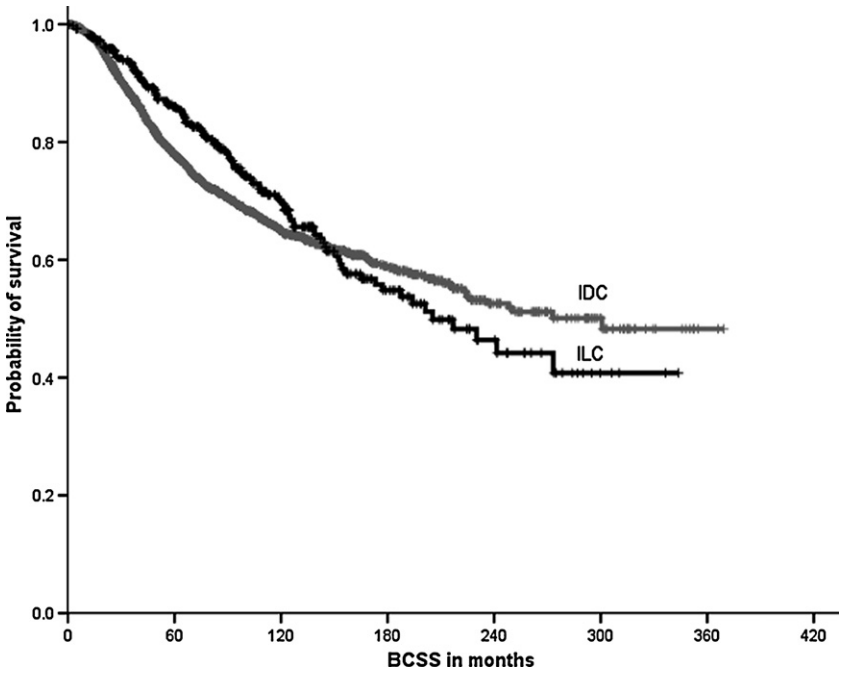

Fig. 1A – Relation between invasive lobular carcinoma (ILC; 407 cases) and invasive duct carcinoma (IDC; 2779 cases) and cancer specific survival (BCSS) in the whole series. The number of patients at risk for ILC and IDC was as follows: 218 and 1125 at 60 months; 106 and 437 at 120 months; 41 and 163 at 180 months; 14 and 56 at 240 months and 2 and 15 at 300 months of follow-up, respectively.

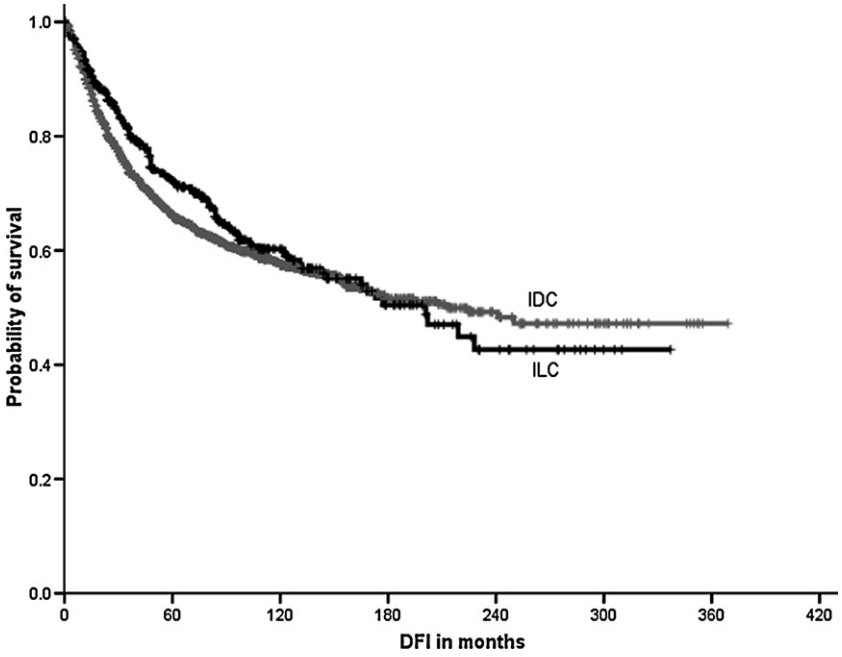

Fig. 1B – Relation between ILC and IDC and disease-free interval (DFI) in the whole series.

6. Discussion

The management of primary breast cancer has changed over the years, and systemic adjuvant therapy is now commonplace. These recent advances in breast cancer treatment have made recognition and characterisation of different prognostic groups mandatory. The current study demonstrates that invasive lobular carcinoma (ILC) has distinctive clinical and biologic characteristics compared to the more common and more extensively studied duct carcinoma of no special type (IDC). ILC is more likely to be associated with pathological variables of good prognosis such as lower grade, absence of

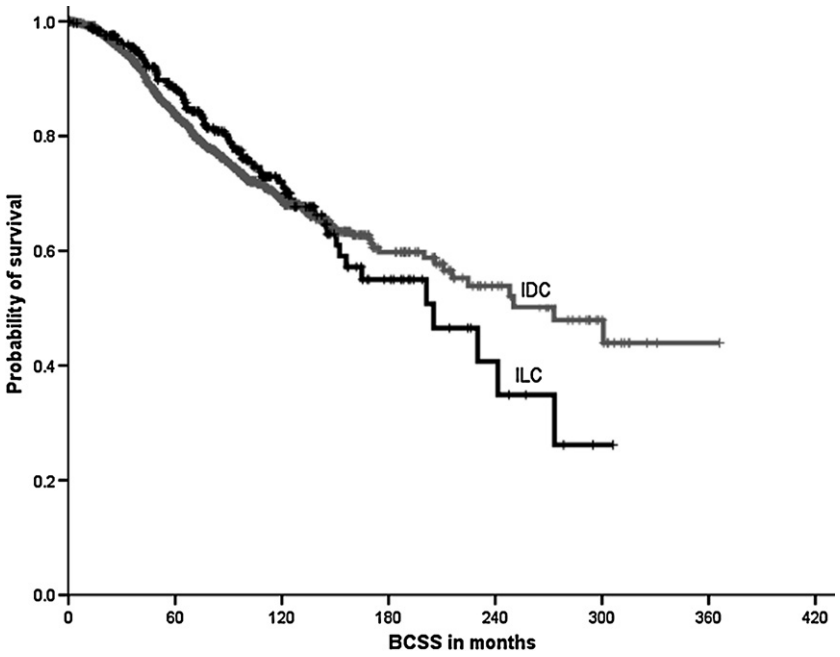

Fig. 1C – Relation between ILC and IDC and BCSS in the ER positive subgroup [1863 cases; 301 ILC and 1562 IDC patients] (LR = 0.03, $p = 0.85$). The number of patients at risk for ILC and IDC was as follows: 141 and 597 at 60 months; 53 and 180 at 120 months; 15 and 57 at 180 months, and 5 and 24 at 240 months of follow-up, respectively.

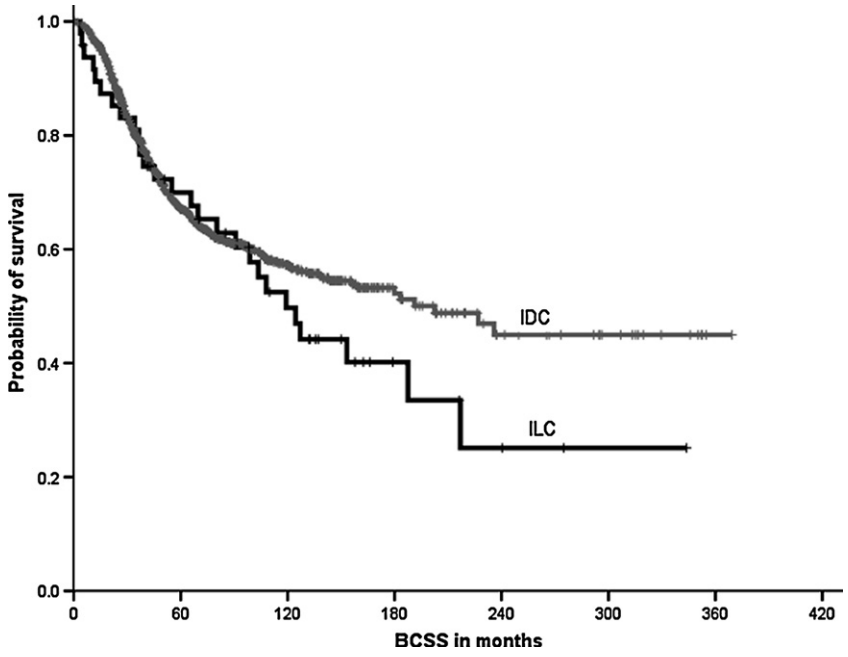

Fig. 1D – Relation between ILC and IDC and BCSS in the ER negative subgroup [1021 cases; 48 ILC and 973 IDC patients] (LR = 1.7, $p = 0.19$). The number of patients at risk for ILC and IDC was as follows: 28 and 349 at 60 months; 13 and 132 at 120 months, and 5 and 39 at 180 months of follow-up, respectively.

vascular invasion and positive expression of hormone receptors, and lack of expression of basal CKs, HER2, EGFR, p53 and P-cadherin. The patterns of metastases in ILC were also different from that of IDC.

The incidence of ILC observed in the present study (8%) is in accordance with the range of 5–15% reported in the literature.[1,2] The majority of tumours were of grade 2 and associated with slightly older age, larger size, positive HR and absence of vascular invasion, consistent with previous ILC study populations.[1,14,24,37] In addition, the large number of patients, the single institutional nature of our study population and the follow-up period of up to 30 years strengthen the

Table 3 – Multivariate Cox regression analysis of factors associated with breast cancer specific survival (BCSS) and disease-free interval (DFI)

Predictor	BCSS		DFI	
	Hazards Ratio (95% confidence interval (CI))	*p*-value	Hazards Ratio (95% CI)	*p*-value
Lymph node status[a]	2.2 (1.88–2.66)	<0.001	1.9 (1.63–2.2)	<0.001
Grade	1.66 (1.38–2.01)	<0.001	1.37 (1.2–1.76	<0.001
Size (⩽2 cm versus >2 cm)	1.29 (1.1–1.5)	0.001	1.3 (1.2–1.5)	<0.001
Vascular invasion[b]	1.26 (1.06–1.51)	0.009	1.14 (0.98–1.34)	0.092
ER status	0.8 (0.68–0.8)	0.03	0.99 (0.84–1.2)	0.92
Hormonal therapy (HT)	0.79 (0.5–1.22)	0.29	0.67 (0.46–0.98)	0.039
Tumour type (TT)	1.76 (1.2–2.6)	0.005	1.67 (1.2–2.4)	0.004
TT*TH	**0.71 (0.52–0.98)**	**0.035**	**0.7 (0.53–0.93)**	**0.013**

HT, hormonal therapy given versus not given; TT, IDC versus ILC; TT*HT, an interaction between histologic type (IDC/ILC) and hormonal therapy.

a Lymph node negative versus positive.

b Absent or probable versus definite vascular invasion.

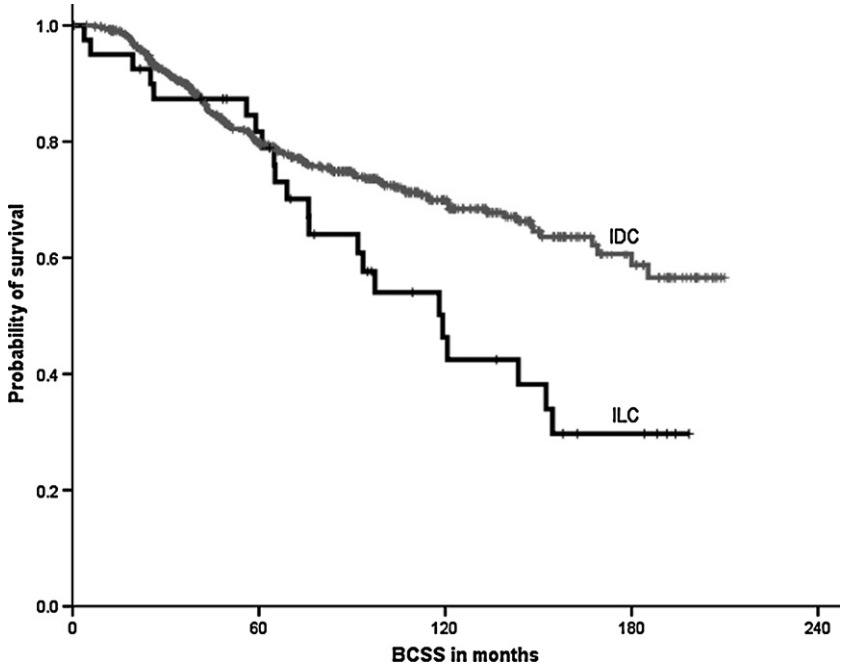

Fig. 2A – Relation between ILC (40) and IDC (600) and BCSS in patients with moderate Nottingham Prognostic Index (NPI) subgroup who did not receive hormonal treatment. The figure shows an association between ILC and poorer survival (LR = 7.6, $p = 0.006$). The number of patients at risk for ILC and IDC was as follows: 29 and 335 at 60 months; 12 and 144 at 120 months, and 5 and 32 at 180 months of follow-up, respectively.

reliability of the results and permit extrapolation of the findings to routine clinical practice.

Our results demonstrated that the metastatic pattern for ILC differs from that of IDC. ILC was less likely to affect the lungs, CNS and liver than was IDC. By contrast, bone was more likely to be involved in ILC. Although some studies comparing metastatic patterns of lobular and ductal carcinoma have reported conflicting results, it has been reported that ILC less often involves the lungs and CNS, and liver, but is more likely to involve bone.[1,12,13] It has also been documented that metastases to the gastrointestinal system, gynaecologic organs and peritoneum are more characteristic of lobular carcinoma. However, we were unable to address this issue directly because of limitations in the database. In addition, this study definitively confirms and extends the findings of the previous few studies that had addressed the biologic features of ILC[1,10,25] indicating that ILC are significantly more likely to be steroid receptor positive and lack expression of E-cadherin, P-cadherin, HER2, EGFR and p53 than are IDC. Therefore, together these findings imply that ILC is biologically different from IDC.

The prognosis for ILC compared to IDC is unclear and previous studies showed some conflicting results.[9,14,19–22,24,25] In the present study, the clinical outcome of ILC pa-

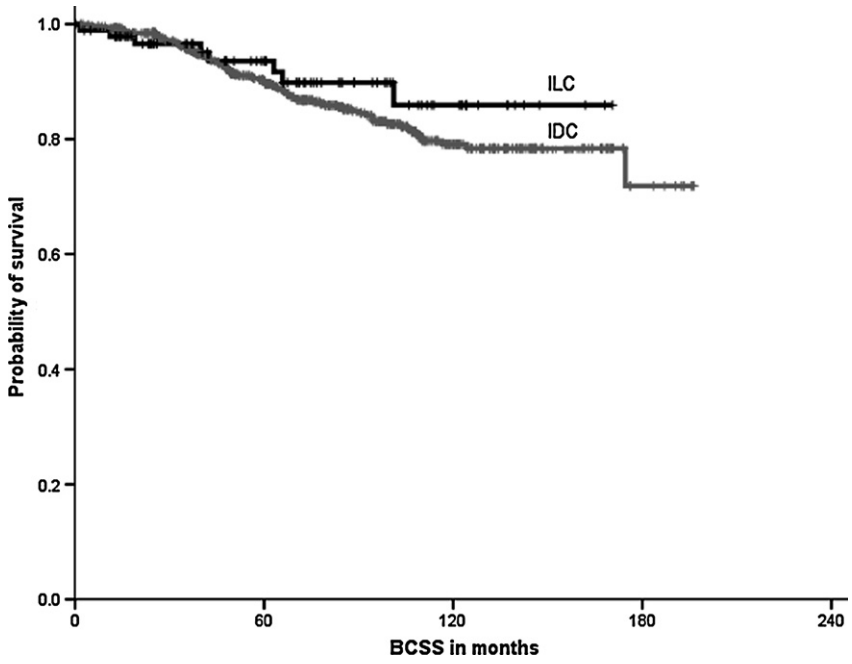

Fig. 2B – Relation between ILC and IDC and BCSS in patients with moderate NPI subgroup who received hormonal treatment (759 patients; 95 ILC and 664 IDC patients). The figure shows improved survival of ILC patients (LR = 0.82, $p = 0.36$). The number of patients at risk for ILC (95) and IDC (664 patients) was as follows: 36 and 226 at 60 months and 8 and 67 at 120 months of follow-up, respectively).

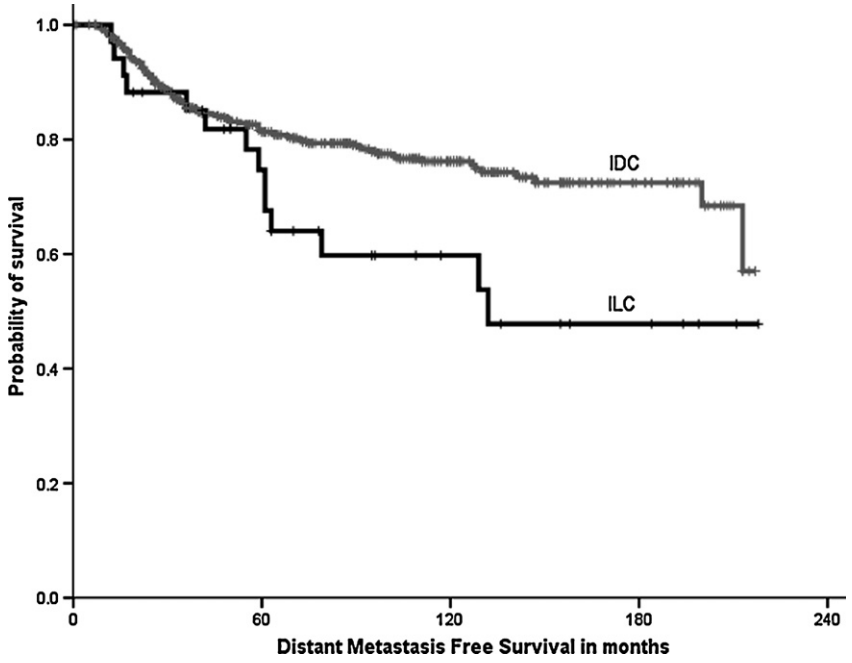

Fig. 2C – Relation between ILC and IDC and distant metastasis free survival in the moderate NPI group who did not receive hormonal treatment. The figure shows association between ILC and worse DM free survival (LR = 5.8, $p = 0.02$).

tients was not different from that of patients with IDC in the overall series. However, when stratified into matched groups, ILC tends to show a worse long-term outcome 'prognosis' with a higher incidence of development of DM, recurrences and breast cancer mortality. Therefore, the fact that ILC has more favourable prognostic factors does not translate into a survival advantage for patients with ILC. The association with a relatively larger size and the reported higher rate of false-negative LN by histologic examination in ILC could cause a general under-staging of this histologic type at the time of surgery. The indolent nature of ILC might possibly lead to a longer period of growth

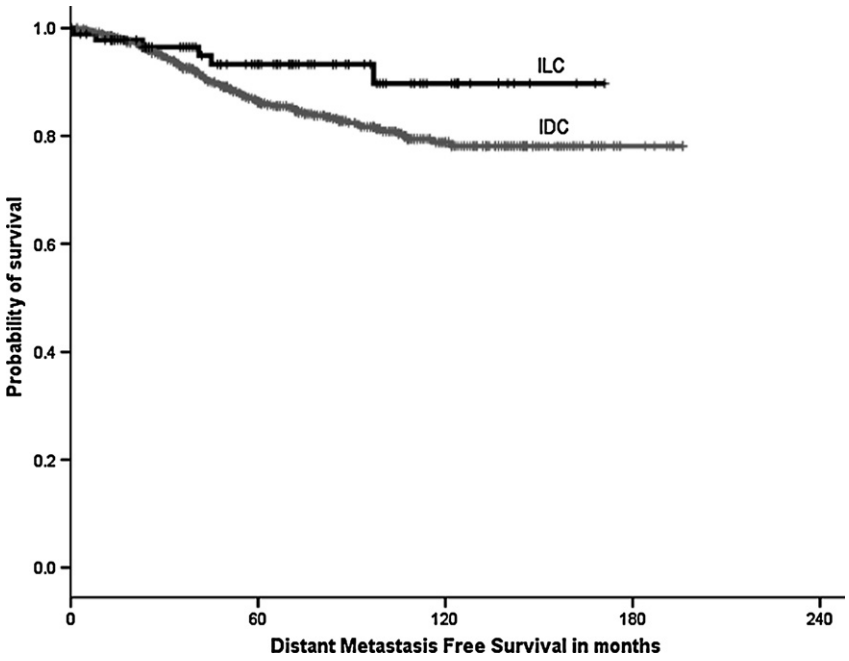

Fig. 2D – Relation between ILC (95) and IDC (664 patients) and distant metastasis free survival in the moderate NPI group who received hormonal treatment. The figure shows association between ILC and better DM free survival (LR = 4.7, $p = 0.03$).

before detection. ILC has lower proliferative activity than IDC.[1,10] Gene microarrays of breast cancer have also demonstrated that ILC and IDC have distinct genomic and expression profiles with significant difference in the expression of some genes involved in cell growth, cell adhesion/motility and immune response. These differences may underlie the observed phenotypic and clinical characteristics of the two tumour types.

An important observation in this study is the tendency of ILC to show slightly better or similar outcome to IDC in the early intervals following detection; however, long-term follow-up shows an obvious tendency to develop late recurrence and worse outcome. Importantly, this characteristic pattern of survival was independent of ER status. The observed outcome of ILC in our series is comparable to that of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL) with indolent behaviour that continues to decline in survival overtime in a nearly linear pattern, while that of IDC shows early events in the first 10 years which level off after that (patients either die early or survive similar to the pattern of survival in high grade lymphomas). These results may be consistent with those of Bouvet and colleagues,[38] who reported that many local recurrences of breast cancer following conservation therapy are late events. Another potential explanation is that ILC patients may have received less adjuvant treatment.

In ILC patients, although several prognostic factors showed an association with survival, only LN stage and grade retained their independent prognostic significance after adjustment for other established clinicopathologic variables confirming the importance of histologic grading of ILC.[30] In the current study, we analysed the effect of systemic adjuvant endocrine therapy on the long-term clinical outcome of ILC as compared to IDC patients. Our results showed that HT improves the clinical outcome of ILC patients as compared to IDC, which is not surprising given the strong association with hormone receptors (HR)[1,8–10,14,24,37] and the observation that menopausal hormone replacement therapy increases risk of ILC and mixed ILC/IDC compared to pure IDC.[4] An association between HT and a better outcome was also noticed amongst ILC patients both in the whole tumour series and in the different subgroups. To our knowledge, this is the first report that addresses the correlation between HT and long-term outcome in ILC in such a large cohort of patients. Although a few studies did not report a good response of ILC to HT, probably due to the relatively few number of cases,[39,40] other studies have shown a better response to adjuvant HT in ILC.[8,26] However, because our results are based on a retrospective study, they ideally need to be confirmed in a randomised controlled trial of endocrine treatment with long-term follow-up.

ILC is less responsive to chemotherapy,[8,16,25,29] lacks the benefit of HER2 targeted therapy[1,30,31] and is more often HR positive. In addition, previous studies have reported that HT is a good alternative option for elderly patients who are poor candidates for primary cytotoxic chemotherapy.[25,41] Overall, these results indicate that the role of endocrine therapy in ILC should be strongly considered to improve patients' outcome. Moreover, although in our dataset, there was no significant difference between the two tumour types regarding the incidence of contralateral breast cancer, bilateral involvement is reported to be nearly double that in women with IDC in several other studies.[1] This finding could make a compelling case for the use of HT to prevent the development of contralateral breast cancer in women with ILC.

7. Conclusion

Our results show clearly that ILC and IDC are distinct entities with different clinical courses and different biologic

phenotypes. Although no clinically meaningful differences in survival are observed, ILC showed a better response to adjuvant HT. These are important observations as these tumours are more often hormone-receptor positive, typically lack HER2 expression and show poor response to CT limiting the range of other relevant adjuvant therapies.

Conflict of interest statement

None declared.

REFERENCES

1. Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. *Breast Cancer Res* 2004;**6**:R149–56.
2. Martinez V, Azzopardi JG. Invasive lobular carcinoma of the breast: incidence and variants. *Histopathology* 1979;**3**:467–88.
3. Li CI, Anderson BO, Daling JR, Moe RE. Trends in incidence rates of invasive lobular and ductal breast carcinoma. *JAMA* 2003;**289**:1421–4.
4. Reeves GK, Beral V, Green J, Gathani T, Bull D. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol* 2006;**7**:910–8.
5. Yoder BJ, Wilkinson EJ, Massoll NA. Molecular and morphologic distinctions between infiltrating ductal and lobular carcinoma of the breast. *Breast J* 2007;**13**:172–9.
6. Korkola JE, DeVries S, Fridlyand J, et al. Differentiation of lobular versus ductal breast carcinomas by expression microarray analysis. *Cancer Res* 2003;**63**:7167–75.
7. Cleton-Jansen AM. E-cadherin and loss of heterozygosity at chromosome 16 in breast carcinogenesis: different genetic pathways in ductal and lobular breast cancer? *Breast Cancer Res* 2002;**4**:5–8.
8. Tubiana-Hulin M, Stevens D, Lasry S, et al. Response to neoadjuvant chemotherapy in lobular and ductal breast carcinomas: a retrospective study on 860 patients from one institution. *Ann Oncol* 2006;**17**:1228–33.
9. Silverstein MJ, Lewinsky BS, Waisman JR, et al. Infiltrating lobular carcinoma. Is it different from infiltrating duct carcinoma? *Cancer* 1994;**73**:1673–7.
10. Coradini D, Pellizzaro C, Veneroni S, Ventura L, Daidone MG. Infiltrating ductal and lobular breast carcinomas are characterised by different interrelationships among markers related to angiogenesis and hormone dependence. *Br J Cancer* 2002;**87**:1105–11.
11. Ferlicot S, Vincent-Salomon A, Medioni J, et al. Wide metastatic spreading in infiltrating lobular carcinoma of the breast. *Eur J Cancer* 2004;**40**:336–41.
12. Winston CB, Hadar O, Teitcher JB, et al. Metastatic lobular carcinoma of the breast: patterns of spread in the chest, abdomen, and pelvis on CT. *AJR Am J Roentgenol* 2000;**175**:795–800.
13. Lamovec J, Bracko M. Metastatic pattern of infiltrating lobular carcinoma of the breast: an autopsy study. *J Surg Oncol* 1991;**48**:28–33.
14. Sastre-Garau X, Jouve M, Asselain B, et al. Infiltrating lobular carcinoma of the breast. Clinicopathologic analysis of 975 cases with reference to data on conservative therapy and metastatic patterns. *Cancer* 1996;**77**:113–20.
15. Paumier A, Sagan C, Campion L, et al. Accuracy of conservative treatment for infiltrating lobular breast cancer: a retrospective study of 217 infiltrating lobular carcinomas and 2155 infiltrating ductal carcinomas. *J Gynecol Obstet Biol Reprod (Paris)* 2003;**32**:529–34.
16. Cocquyt V, Van Belle S. Lobular carcinoma in situ and invasive lobular cancer of the breast. *Curr Opin Obstet Gynecol* 2005;**17**:55–60.
17. Ashikari R, Huvos AG, Urban JA, Robbins GF. Infiltrating lobular carcinoma of the breast. *Cancer* 1973;**31**:110–6.
18. Mate TP, Carter D, Fischer DB, et al. A clinical and histopathologic analysis of the results of conservation surgery and radiation therapy in stage I and II breast carcinoma. *Cancer* 1986;**58**:1995–2002.
19. Vo TN, Meric-Bernstam F, Yi M, et al. Outcomes of breast-conservation therapy for invasive lobular carcinoma are equivalent to those for invasive ductal carcinoma. *Am J Surg* 2006;**192**:552–5.
20. Molland JG, Donnellan M, Janu NC, Carmalt HL, Kennedy CW, Gillett DJ. Infiltrating lobular carcinoma – a comparison of diagnosis, management and outcome with infiltrating duct carcinoma. *Breast* 2004;**13**:389–96.
21. Korhonen T, Huhtala H, Holli K. A comparison of the biological and clinical features of invasive lobular and ductal carcinomas of the breast. *Breast Cancer Res Treat* 2004;**85**:23–9.
22. Casolo P, Raspadori A, Drei B, et al. [Natural history of breast cancer: lobular carcinoma versus ductal carcinoma in our experience]. *Ann Ital Chir* 1997;**68**:43–7. discussion 48.
23. Peiro G, Bornstein BA, Connolly JL, et al. The influence of infiltrating lobular carcinoma on the outcome of patients treated with breast-conserving surgery and radiation therapy. *Breast Cancer Res Treat* 2000;**59**:49–54.
24. Toikkanen S, Pylkkanen L, Joensuu H. Invasive lobular carcinoma of the breast has better short- and long-term survival than invasive ductal carcinoma. *Br J Cancer* 1997;**76**:1234–40.
25. Cristofanilli M, Gonzalez-Angulo A, Sneige N, et al. Invasive lobular carcinoma classic type: response to primary chemotherapy and survival outcomes. *J Clin Oncol* 2005;**23**:41–8.
26. du Toit RS, Locker AP, Ellis IO, et al. An evaluation of differences in prognosis, recurrence patterns and receptor status between invasive lobular and other invasive carcinomas of the breast. *Eur J Surg Oncol* 1991;**17**:251–7.
27. Dixon JM, Anderson TJ, Page DL, Lee D, Duffy SW. Infiltrating lobular carcinoma of the breast. *Histopathology* 1982;**6**:149–61.
28. du Toit RS, Locker AP, Ellis IO, Elston CW, Nicholson RI, Blamey RW. Invasive lobular carcinomas of the breast – the prognosis of histopathological subtypes. *Br J Cancer* 1989;**60**:605–9.
29. Mathieu MC, Rouzier R, Llombart-Cussac A, et al. The poor responsiveness of infiltrating lobular breast carcinomas to neoadjuvant chemotherapy can be explained by their biological profile. *Eur J Cancer* 2004;**40**:342–51.
30. Bane AL, Tjan S, Parkes RK, Andrulis I, O'Malley FP. Invasive lobular carcinoma: to grade or not to grade. *Mod Pathol* 2005;**18**:621–8.
31. Cocquyt VF, Blondeel PN, Depypere HT, et al. Different responses to preoperative chemotherapy for invasive lobular and invasive ductal breast carcinoma. *Eur J Surg Oncol* 2003;**29**:361–7.
32. Galea MH, Blamey RW, Elston CE, Ellis IO. The Nottingham Prognostic Index in primary breast cancer. *Breast Cancer Res Treat* 1992;**22**:207–19.
33. Abd El-Rehim DM, Ball G, Pinder SE, et al. High-throughput protein expression analysis using tissue microarray technology of a large well-characterised series identifies biologically distinct classes of breast cancer confirming recent cDNA expression analyses. *Int J Cancer* 2005;**116**:340–50.
34. Rakha EA, Putti TC, Abd El-Rehim DM, et al. Morphological and immunophenotypic analysis of breast carcinomas with basal and myoepithelial differentiation. *J Pathol* 2006;**208**:495–506.

35. Ellis IO, Galea M, Broughton N, Locker A, Blamey RW, Elston CW. Pathological prognostic factors in breast cancer. II. Histological type. Relationship with survival in a large study with long-term follow-up. *Histopathology* 1992;**20**:479–89.
36. Lee ET, Desu MM, Gehan EA. A Monte Carlo study of the power of some two-sample tests. *Biometrika* 1975;**62**:425–32.
37. Chung MA, Cole B, Wanebo HJ, Bland KI, Chang HR. Optimal surgical treatment of invasive lobular carcinoma of the breast. *Ann Surg Oncol* 1997;**4**:545–50.
38. Bouvet M, Ollila DW, Hunt KK, et al. Role of conservation therapy for invasive lobular carcinoma of the breast. *Ann Surg Oncol* 1997;**4**:650–4.
39. Jirstrom K, Ryden L, Anagnostaki L, et al. Pathology parameters and adjuvant tamoxifen response in a randomised premenopausal breast cancer trial. *J Clin Pathol* 2005;**58**:1135–42.
40. Smith DB, Howell A, Wagstaff J. Infiltrating lobular carcinoma of the breast: response to endocrine therapy and survival. *Eur J Cancer Clin Oncol* 1987;**23**: 979–82.
41. Horobin JM, Preece PE, Dewar JA, Wood RA, Cuschieri A. Long-term follow-up of elderly patients with locoregional breast cancer treated with tamoxifen only. *Br J Surg* 1991;**78**:213–7.