Adequacy of diagnostic tests and surgical management of symptomatic invasive lobular carcinoma of the breast

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ABSTRACT

INTRODUCTION Invasive lobular carcinoma (ILC) presents diagnostic and therapeutic challenges as it produces subtle radiological changes. It has been suggested that it is not suitable for breast conserving surgery (BCS). The aim of this study was to ascertain the diagnostic adequacy of modern mammography and ultrasonography in the context of a fast track symptomatic diagnostic clinic in the UK. It also sought to compare the mastectomy, re-excision and BCS rates for ILC with those for invasive ductal carcinoma (IDC).

METHODS A retrospective analysis of prospectively collected data was carried out on all new symptomatic cancers presenting to the one-stop diagnostic clinic of a single breast unit between 1998 and 2007.

RESULTS Compared with IDC, ILC was significantly larger at presentation (46mm vs 25mm), needed re-excision after BCS more often (38.8% vs 22.3%) and required mastectomy more frequently (58.8% vs 40.8%). Although mammography performs poorly in diagnosing ILC compared with IDC, when combined with ultrasonography, sensitivity of the combined imaging was not significantly different between these two histological types.

CONCLUSIONS Provided ultrasonography is performed, standard radiological imaging is adequate for initial diagnosis of symptomatically presenting ILC but some additional preoperative workup should clearly be employed to reduce the higher number of reoperations for this histological type.

KEYWORDS

Invasive lobular carcinoma – Invasive ductal carcinoma – Breast ultrasonography – Mammography – Breast conserving surgery

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Invasive lobular carcinoma (ILC) of the breast is characterised pathologically by tumour cells infiltrating the breast parenchyma in single files without any substantial stromal reaction.¹ As a result, ILC often produces a diffuse thickening of the breast tissue rather than a discrete lump, which could cause delay in symptomatic presentation. According to some reports, the incidence of ILC has increased in recent years, possibly stimulated by an increased use of hormone replacement therapy.² This potential delay in symptomatic presentation (and putatively in diagnosis) combined with the increased incidence render ILC a challenge for modern healthcare services.

Compared with ductal carcinoma, the radiological appearance of ILC is considered to be more subtle.^{3,4} ILC related mammographic abnormalities usually lack microcalcifications and are not always visible on all mammographic views.^{5,6} Consequently, it is frequently reported that ILC is more difficult to diagnose in the screening setting when mammography is used alone.^{7–10}

On the other hand, it is not known whether the efficacy of standard radiological imaging combining modern mammography and breast ultrasonography is sufficient to raise the index of suspicion in those patients who present with symptoms from ILC. The issue is very important since mammography and breast ultrasonography continue to be the standard diagnostic imaging modalities for initial diagnosis of patients presenting to fast track one-stop clinics in the UK despite the fact that contrast enhanced magnetic resonance imaging (MRI) mammography is being used increasingly for preoperative workup of patients with a diagnosis of ILC.¹¹

In addition, ILC is reputed to be larger at presentation, requiring mastectomy rather than breast conserving surgery (BCS) more often than ductal carcinoma.^{9,12} In most previous studies, however, the cohort of reported cases includes screen detected as well as symptomatically presenting cases and a conclusion regarding patients presenting with a 'lump' cannot be reached without significant bias.

The aim of this study was to examine whether our prospectively collected data from St Mary's Hospital, London, support these commonly held views about ILC in symptomatic cases and to investigate whether owing to its unique characteristics, clinical approach to this histological type of breast cancer should differ.

Methods

This study is based on analysis of a prospectively accrued database of a single breast cancer unit. Radiological, histological and clinical characteristics of all new symptomatically presenting breast cancer patients were collected on the Thames Cancer Registry database between April 1998 and December 2007. Data on histological type for a small number of patients was confirmed retrospectively as the initial histopathology report was ambiguous, particularly with respect to a number of mixed type tumours or special histological types. Epithelial cadherin immunohistochemical staining was performed at the discretion of the consultant histopathologist when there was doubt about the diagnosis of lobular carcinoma. Ninety-eight per cent of this cohort of consecutive symptomatic breast cancer patients had a preoperative diagnosis made on core biopsy and/or fine needle aspiration. All patients who did not undergo surgery upfront had their diagnosis made on core biopsy.

Analysis of histological size at presentation, mastectomy and re-excision rates was performed on those cases that had surgery upfront (ie excluding cases that received neoadjuvant medical therapy or had no surgery as part of their treatment).

Surgical treatment

Decision regarding the type of surgery was based on the size of the primary tumour at presentation according to the preoperative ultrasonography, adhering to strict protocols. Tumours measuring up to 30mm on ultrasonography were considered suitable for BCS irrespective of histological type, provided mammography did not clearly show a much larger total tumour size. These patients were offered the choice between BCS and mastectomy, and the vast majority chose BCS. Multifocality within a 30mm area was not considered a contraindication to BCS whereas multicentricity was an indication for mastectomy. A number of tumours, especially ILC, were difficult to measure on ultrasonography. In these cases, the decision to perform BCS or mastectomy was based on mammography and clinical estimation of tumour size. MRI mammography for ILC cases became routine in our unit after 2007.

Wide excision was performed from the skin down to the pectoral fascia. Anterior and posterior margins were therefore not re-excised unless tumour was present at the margin. In cases where all invasive tumour and in situ components were excised with a minimum of 5mm of clear circumferential margin, the procedure was considered acceptable even if the total histological size of the tumour was up to 40mm. For tumours that were found to

measure greater than 40mm on final histology but were excised with a 5mm or greater margin, a recommendation was made to the patient that she would probably benefit from a completion mastectomy. A few patients accepted this recommendation. Circumferential margins of 4mm or less were always re-excised or completion mastectomy was performed.

Histological type

All patients with a new, symptomatic, invasive breast cancer diagnosis between April 1998 and December 2007 were included in the study analysis. Histological types were divided into four groups: ILC, IDC not otherwise specified, IDC with mixed pattern and special type ductal cancers. Tubular, adenoid cystic, medullary, papillary and mucinous carcinomas were included under special type cancers. Encysted papillary cancer was considered to represent in situ disease and was therefore excluded. Invasive ductal cancers with lobular features were included under mixed tumours, as were mixed IDCs and tubulolobular IDCs. All types of ILC were included under the same single category of ILC. Epithelial cadherin immunohistochemical staining was performed at the discretion of the consultant pathologist.

Radiological assessment

According to our protocol, all symptomatic patients apart from those with diffuse mastalgia as their only symptom underwent ultrasonography and those over the age of 35 years also had mammography. Data on the BI-RADS® (Breast Imaging Reporting and Data System; American College of Radiology, Reston, VA, US) code used by the radiologist during the patient's initial presentation at the one-stop breast clinic were collected prospectively between April 1998 and December 2007. Codes were collected individually for mammography and breast ultrasonography using the BI-RADS® scale (M1–M5) for mammography¹³ and a similar scale for breast ultrasonography (U1–U5). These codes were recorded by the radiologist on the hospital's electronic reporting system before cytological or histological confirmation and could not be amended afterwards. Preoperative MRI mammography was not performed in this cohort of patients.

Size at presentation

This was the total histological size of the tumour (including any in situ ductal component) on surgical excision as measured by the pathologist. It did not include LCIS and according to the protocols of the unit at the time, these lesions were not deliberately excised during therapeutic operations. Analysis of size at presentation only included those patients with invasive breast cancer who underwent surgery upfront.

Re-excision data

Re-excision was performed in all cases where one or more of the circumferential margins of the initial BCS were 4mm or less. Margin width was treated the same whether it was from DCIS or invasive cancer. Re-excisions of the

anterior or posterior margins were performed only if they were involved. In the latter cases, a corresponding portion of pectoralis major muscle or skin was excised. A number of patients had mastectomy as re-excision.

Statistical analysis

Statistical analysis was performed using SPSS® version 17 (SPSS, Chicago, IL, US). For categorical variables, the Pearson chi-squared and Fisher's exact tests were used to assess differences between the frequencies. Tumour sizes were compared using a two-tailed t-test. Any p -value of <0.05 was considered statistically significant.

Results

Age and histological tumour size

As shown in Table 1, there was no statistically significant difference in age at presentation among the different histological types of breast cancer. Table 1 also shows the mean total tumour size of different histological types that presented symptomatically to our unit. The mean size of ILC tumours at symptomatic presentation was 46mm compared with 25mm for patients with IDC, 32mm for mixed tumours and 19mm for special histological type tumours. When comparing ILC with IDC tumours, the difference in size was found to be statistically significant ($p<0.05$).

Radiological diagnosis

The percentages of the various histological types of breast cancers that were prospectively allocated the codes M4/M5 in mammography are shown in Table 2. ILC tumours were given the codes M4/M5 less frequently than IDC tumours. Consequently, the sensitivity of mammography alone in providing a suspicious code for ILC was 0.67 compared with 0.80 for IDC. This difference was statistically significant ($p=0.003$).

The percentages of breast cancers that were given the codes U4/U5 in breast ultrasonography for each histological type are also shown in Table 2. There was no statistically significant difference in the proportion of ILC cases that were allocated U4/U5 when compared with IDC (sensitivity 0.91 for ILC and 0.92 for IDC, $p=0.565$).

Although the sensitivity of mammography in providing a suspicious code for ILC was clearly inferior to that for IDC, the percentage of patients who had at least one suspicious investigation was similar: 92.8% for IDC and 91.8% for ILC ($p=0.714$).

Type of operation and mastectomy rate

Among the patients who underwent surgery as their first treatment modality, 58.8% of those with ILC eventually had to have a mastectomy compared with 40.8% of IDC patients (Table 3). This difference was statistically significant ($p<0.005$). Special type cancers did not have a significantly lower mastectomy rate than IDCs ($p=0.265$). Table 3

Table 1 Mean age of presentation of various histological types of breast cancer and mean size of excised tumours in histological specimens

	ILC	IDC	Mixed	Special type
Mean age in years (range)	60 (35–91)	59 (25–83)	66 (36–85)	60 (34–95)
Mean size in mm (range)	46* (5–170)	25 (1–105)	32 (6–68)	19 (4–57)

ILC = invasive lobular carcinoma; IDC = invasive ductal carcinoma

*Larger than IDC (two-tailed t-test, $p<0.05$)

Table 2 Number of mammograms and ultrasonography scans performed in this cohort of 904 consecutive cases of invasive breast carcinoma presenting in a symptomatic breast clinic

	Total	ILC	IDC	Mixed	Special type
Number of cases	904	103	687	54	59
Number of mammograms	843	97	641	51	53
Mammograms graded M4/M5	78.3%	67.0%*	80.2%*	78.4%	73.6%
Number of ultrasonography scans	884	97	645	49	52
Ultrasonography graded U4/U5	87.2%	90.7%	92.4%	89.8%	78.8%

ILC = invasive lobular carcinoma; IDC = invasive ductal carcinoma

*The difference in the percentage of mammograms graded as M4/M5 between patients with ILC and those with IDC was statistically significant (chi-squared test, $p=0.003$).

Table 3 Number of symptomatic cases undergoing primary surgery. Patients who received any form of neoadjuvant medical treatment are excluded.

	Total	ILC	IDC	Mixed	Special type
Total	701	80	527	45	49
Mastectomy as first operation	224 (32.0%)	31 (38.8%)	155 (29.4%)	23 (51.1%)	15 (30.6%)
BCS as first operation	477 (68.0%)	49 (61.3%)	372 (70.6%)	22 (48.9%)	34 (69.3%)
Mastectomy as final operation	303 (43.2%)	47 (58.8%)*	215 (40.8%)*	25 (55.6%)	16 (32.7%)
BCS as final operation	398 (56.8%)	33 (41.3%)	312 (59.2%)	20 (44.4%)	33 (67.3%)

ILC = invasive lobular carcinoma; IDC = invasive ductal carcinoma; BCS = breast conserving surgery
*The difference in the percentage of ILC and IDC patients who underwent mastectomy as their final operation was statistically significant (chi-squared test, $p=0.002$).

Table 4 Number of patients undergoing BCS, re-excision and completion mastectomy by histological type

	Total	ILC	IDC	Mixed	Special type
BCS as first operation	477	49	372	22	34
Re-excision or completion mastectomy	111	19 (38.8%)*	83 (22.3%)*	5 (22.7%)	4 (11.8%)
Completion mastectomy	79	16 (32.7%)	60 (16.1%)	2 (9.1%)	1 (2.9%)
Re-excision to clear margins	32	3 (6.1%)	23 (6.2%)	3 (13.6%)	3 (8.8%)
BCS as final operation	398	33 (67.3%)	312 (83.9%)	20 (90.9%)	33 (97.1%)

ILC = invasive lobular carcinoma; IDC = invasive ductal carcinoma; BCS = breast conserving surgery
*The difference in re-excision rate between ILC and IDC was statistically significant (chi-squared test, $p=0.002$).

shows the number of mastectomies performed as a final operation in different histological types.

Of the patients with ILC who had surgery upfront, 61.3% initially underwent BCS whereas for patients with IDC, it was 70.6% (Table 3). This trend was not statistically significant ($p=0.09$).

Re-excision to clear margins and completion mastectomy

All patients undergoing BCS as a final operation achieved clear posterior and anterior margins, and circumferential margins of >5mm. Table 4 shows the number of patients who underwent a minimum of two therapeutic operations (whether that included re-excision or completion mastectomy). Patients with ILC had a re-excision rate of 38.8% compared with 22.3% for patients with IDC. This difference was statistically significant ($p=0.002$).

Local recurrence as first event in ILC patients undergoing BCS

BCS was attempted upfront in 49 of the 80 patients with ILC and it was the final operation in 33 of these. The remaining 16 patients underwent mastectomy at re-excision (Tables 3 and 4). To date, one of the 33 patients with BCS as a final operation has developed local recurrence as a first event.

Previous presentations of patients with ILC

The electronic records of all ILC patients were examined retrospectively to ascertain whether their cancer might have been missed on a previous occasion. Only three patients had a previous appointment at our breast clinic, two of them for symptoms affecting the contralateral breast to the one that developed ILC subsequently. The third patient underwent open surgical biopsy for a lump that was clinically suspicious because no definitive histological diagnosis could be made on core biopsy. The open surgical biopsy showed sclerosing adenosis but the patient presented with ILC in the same quadrant two years later. Another patient had presented at a neighbouring hospital, where she received a benign diagnosis for a lump that was shown subsequently to be ILC at our unit six months later. The latter are the only two patients with ILC in this cohort that may have had a delay in diagnosis.

Delay in diagnosis in non-ILC patients was not examined in this study.

Discussion

Larger tumour size at presentation of ILC compared with other tumours has been described previously. In a study of a large cohort, Sastre-Garau *et al* reported that 19% of

patients with ILC had T3 tumours compared with 12% of non-ILC patients but their cohort included screen detected as well as symptomatic cancers.⁸ Their results do not reflect the magnitude of the difference in symptomatic patients; our results suggest that when ILC presents symptomatically, it is almost twice as large as other histological types of invasive breast cancer. As a result, according to our data, ILC will require mastectomy more often than IDC. The incidence of ILC in our series was 8.9% of all new breast cancers, which is very similar to some other recent studies.⁹ Molland *et al* reported very similar findings in terms of re-excision, mastectomy rates and overall incidence.⁹

Some authors have postulated that ILC is generally larger at diagnosis because it may have been missed at initial symptomatic presentation, thereby allowing the tumour to grow until the patient re-presents after an interval.⁸ However, in our cohort of 103 consecutive patients with ILC, only 4 had been seen previously at a breast clinic. In two of these cases, the patients presented with symptoms affecting the contralateral breast to the one that developed ILC subsequently so there were in fact only two patients with ILC in our cohort who may have had a delay in diagnosis.

Although there is anecdotal evidence that ILC is overrepresented in breast cancer patients who experience a delay in diagnosis, the number of these cases cannot account for the differences in size at presentation in our study. Our results can only be explained by the fact that ILC causes symptoms when it reaches a size much larger than other histological types of breast cancer.

Surprisingly, combined classical breast imaging modalities in the fast track breast clinic setting were as good in detecting suspicious radiological signs in cases of ILC as in patients with IDC. Mammography alone was clearly inferior in detecting ILC but when combined with high frequency ultrasonography in the hands of a specialist breast radiologist, the overall sensitivity was no different from that in IDC. This is in agreement with previous reports, suggesting that the addition of ultrasonography increases the sensitivity of diagnostic imaging.^{4,9,10} The shortcomings of mammography in detecting ILC have been reported previously by other authors.^{6,9,14}

In this study, patients with ILC required mastectomy more often than patients with IDC. This is most probably a direct consequence of the fact that ILC tumours were almost twice as large at presentation than IDC tumours. Given that the surgeons were not blinded to the histological diagnosis when the type of operation was discussed with the patient, one could argue that the surgeons could be biased against BCS, knowing that they were dealing with ILC. For this reason, our paper also presents the number of attempted BCS operations and re-excisions.

Our results clearly show that the proportion of patients undergoing BCS as their initial procedure was not statistically different between ILC and IDC cohorts. They also show that a significantly greater proportion of ILC cases had to undergo secondary operations for margin clearance or mastectomy, implying that the imaging modalities used

here underestimated tumour size in ILC more than in IDC. Unfortunately, we do not have any direct data on the pre-operative tumour size as this was not recorded by the initial radiologist on diagnosis for the majority of ILC patients. This could be attributed to the fact that although ultrasonography can diagnose ILC, the ultrasonography changes often merge with the normal breast parenchyma, making it impossible for the radiologist to give any accurate measurement of the size of the lesion. Consequently, prospective collection of preoperative tumour size was left blank in our database for many tumours, particularly ILC.

An increased re-excision rate in ILC patients compared with IDC cases was also reported by O'Sullivan *et al* although they performed re-excisions in a higher proportion of patients overall.¹² Similar re-excision rates were also reported by Molland *et al*.⁹ Re-excision rates depend on the target margin width and ours is in concordance with other reports in the literature when a 5mm margin was aimed for.¹⁴ Our data show that when compared with IDC patients, almost twice as many ILC patients undergoing BCS have at least one re-excision when a 5mm radial margin is required. A meta-analysis in 2010 suggested that with the use of modern adjuvant therapies, excellent local control can be achieved with narrower excisions and margin widths of only 1mm.¹⁵ It is therefore probable that re-excision rates in future will be much lower for breast cancer patients undergoing BCS.

Paradoxically, the combination of mammography and ultrasonography is good enough for diagnostic purposes but grossly inadequate when it comes to estimation of size of ILC tumours. Contrast enhanced MRI mammography is reported to be able to estimate the size of ILC tumours prior to surgery more accurately and has become our standard practice since 2008.^{4,11} Our results certainly support the view that additional imaging is necessary for patients with ILC. Whether that is MRI or other modalities remains to be seen.

Conclusions

In symptomatic patients, the mean size of ILC was much larger than for IDC. As a result, mastectomy was required more often. Although the combination of mammography and breast ultrasonography is good enough for diagnostic purposes for patients presenting symptomatically, these imaging modalities are inadequate in assessing the size of ILC tumours. This is reflected in the higher re-excision rate for this histological type.

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