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Invasive lobular breast cancer. Prognostic significance of histological malignancy grading

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Abstract
Invasive lobular carcinoma (ILC) is the second most reported type of breast cancer in the Danish Breast Cancer Cooperative Group (DBCG). Several histological subtypes exist, with reports of different prognosis. The aim was to present the incidence of ILC in DBCG from 1977–2004, and evaluate tumours regarding diagnosis, histological subtype and grade, and relate to prognosis. Eight hundred and sixty tumours from patients with a diagnosis of ILC or ILC/non-ILC, who underwent breast cancer surgery in the period of 1990–1998, were evaluated. The impact of histological malignancy grade on disease-free survival and overall survival was analysed using a multivariate analysis adjusting for tumour size, hormone receptor status, axillary lymph node status and patient age. The incidence of pure ILC has risen from 5 to 12%, the ILC/non-ILC is constant at 2% of all reported breast cancers in DBCG. Most of the tumours were classical ILC grade II. The majority of the grade III tumours were among the non-classical subtypes, showing a statistically significant worse disease-free and overall survival compared to grade II, regardless of type. The prognosis was the same for grade I and grade II tumours. The number of positive axillary lymph nodes and hormone receptor negative tumours increased among grade III tumours. We conclude that histological malignancy grade has an independent significant impact on the prognosis of ILC, and it should be taken into consideration when planning the postoperative treatment in this group of patients.

The lobular type of breast cancer was first named by Foote and Stewart, the lobular carcinoma in situ (LCIS) in 1941 [1], and the invasive lobular carcinoma (ILC) in 1946 [2]. The invasive lobular carcinoma was accompanied by LCIS in 60% of the cases [2]. Since then, several histological subtypes of ILC have been described; solid, tubulo-lobular, alveolar, signet-ring cell, pleomorphic, a mixed subtype where the different components each constitutes less than 80% of the whole tumour, and finally mixed lobular/ductal presenting with a biphasic pattern [3–11]. The tumour cells are characterised by the same morphology, as in the original classical type, except for the pleomorphic and signet-ring cell variants. Coexisting LCIS is reported with a frequency from 40 to 90% of the cases [2,3,6,9].

The heterogeneity of lobular carcinoma influences the reported frequency of this tumour in the literature, ranging from a few percent to 10–16%, of all invasive breast carcinomas [3,6,11].

Previously ILC was considered to be an aggressive tumour [12], but later on it was shown to have a fairly favourable prognosis [11,13–15] with a 10 year survival of 54–60% [15]. However, some studies show that the prognosis differ significantly among the different histological subtypes, with the alveolar and the tubulo-lobular subtypes having the most favourable prognosis, the pleomorphic subtype having a much worse prognosis, and the classical lobular carcinoma being somewhere in between [3,9,15,16]. The histological malignancy grade was an important factor in predicting survival [17,18].

The Danish Breast Cancer Cooperative Group (DBCG) has collected nationwide data in a clinical database since 1977, and worked out national guidelines to ensure optimal diagnosis and treatment for breast cancer patients [19]. Subtypes of ILC are not specified in the database, and histological malignancy grading of ILC has only been registered since the year 2002. In the DBCG guidelines 2004, unlike

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for the invasive ductal carcinoma (IDC), no action is taken regarding adjuvant therapy based upon histological malignancy grade [19].

The aim of this study is to present the development in the incidences of ILC in DBCG in the period of 1977–2004 for patients in protocol, and for the period of 1990–1998 to evaluate ILC regarding diagnosis, histological subtype and malignancy grade. Further, to relate these data to prognostic data obtained from the DBCG database; tumour size, hormone receptor status, axillary lymph node status and age at time of diagnosis, and their impact on disease-free survival and overall survival.

Materials and methods

Materials

From nine hospitals, data were collected from all patients in DBCG protocol, in the period of 1990–1998 with the diagnosis of pure ILC or ILC mixed with non-ILC (ILC/non-ILC). A total of 1 188 patients fulfilled these criteria, all having breast cancer surgery. Four of the nine hospitals are connected to a programme of organized mammography screening, which started in the beginning of the 1990's, which at the time was not the case in the rest of the country. This partly explains why the patients from the nine selected hospitals are not representative for the whole country regarding tumour size, lymph node status, and hormone receptor status. Pathology reports from the 1 188 patients were collected from the archives of the pathology departments. It was possible to obtain suitable haematoxylin and eosin stained glass slides from formalin fixed, paraffin embedded tumour tissue in 958 of the 1 188 patients.

Methods

All slides were re-examined by light microscopy, by one of the authors (MMT), and difficult cases also by FR. The evaluation of the 958 ILC included recording of the following features: Diagnosis, subclassification of histological subtype, histological malignancy grade, vascular invasion, multifocality and presence of in situ elements, both lobular and ductal. Regarding the diagnosis, three categories were used: Pure ILC including subtypes, ILC/non-ILC and non-ILC. The latter constituted of 98 cases which were excluded from the study, leaving 860 tumours. Both the pure ILC and lobular component in the ILC/non-ILC were classified as either classical type of ILC or non-classical type of ILC. The non-classical ILC were sub-classified in the following histological subtypes: Solid, tubulo-lobular, pleomorphic, signet-ring cell, alveolar and mixed subtype. In the mixed subtype neither of the components constituted of more than 80% of the whole invasive tumour. The criteria used for subclassification of the tumours into the different histological subtypes, including the classical lobular carcinoma, are outlined in the work by Weidner et al. [10] and Ellis et al. [11]. Histological malignancy grading was performed according to the modified Bloom and Richardson grading system [20], where a combination of three histological features is evaluated: Percentage tubule formation, nuclear pleomorphism and mitotic count [18]. Multifocality was defined by at least two tumour foci $\geq$20mm apart.

Database and follow up

The following data was obtained from the DBCG database: Tumour size (pathology measure), hormone receptor status, axillary lymph node status, and age at time of diagnosis. According to the DBCG guidelines, a tumour is considered hormone receptor positive when at least 10% of the nuclei of the tumour cells in the invasive part of the tumour, show a detectable positive reaction in estrogen and/or progesterone receptor staining. Data on follow up was also obtained from the DBCG database; patients enrolled in the DBCG protocols are as a minimum followed once a year, in order to detect possible recurrence. Survival data is accessible for all patients through the Danish Civil Registration System.

Statistical analysis

Associations between grade/type and other characteristics were analyzed by χ^2 test. Median follow-up time was quantified in terms of a Kaplan-Meier estimate of potential follow-up [21]. Overall survival was calculated as the time elapsed from operation until death, irrespective of cause of death. Disease-free survival was defined as the duration of survival without recurrence or any other malignancy. Survival rates were estimated by the Kaplan-Meier method. Overall survival and disease-free survival were analyzed unadjusted using a log rank test. The Cox proportional hazards regression model was applied to assess the relative risk and adjusted relative risk according to grade and to explore interactions. Factors included in the multivariate analyses were tumour size (0–20 mm, 21–50 mm, $>$50 mm), axillary lymph node status (negative, 1–3 positive, $>$3 positive), hormone receptor status (positive, negative, unknown), age ($\leq$35, 36–45, 46–60, 61–65, 66–74) and histological malignancy grade (I, II, III), all being significant in both

univariate and multivariate analysis. Also type (classic, non-classic, mixed, unknown) was considered, but excluded due to lack of independent prognostic significance in the multivariate model. The assumptions of proportional hazards were assessed by log (-log) S plots, Schoenfeld residuals, and by including in the model a time-dependent component for each covariate. The hazard rates of hormone receptor status were not proportional and therefore stratification was used. The level of statistical significance was set to 5%. P-values are two-tailed. Statistical analysis employed SAS 8.2.

Results

The DBCG database on patients in protocolled treatment showed an increase in the number of reported cases of ILC from 297 (5%) (1977–1981) to 3611 (12%) (1989–2004).The entity of ILC/non-ILC was stable at a level of 2% from 1982. The incidences in the period of 1990–1998 varied throughout the country from 7–24%, and the nine selected hospitals showed almost the same range of variation.

The distribution regarding diagnosis in the evaluated material from the nine hospitals is shown in Table I. The 98 tumours that did not meet the criteria for ILC [3,11], were subsequently diagnosed as IDC and excluded from the study, leaving a total of 860 tumours. Most of these, 707 (74%) were pure ILC and a minor part, 153 (16%) were ILC/non-ILC. The non-ILC was mostly of the ductal type, but also a few tumours with a mucinous component were present.

Table II shows the classification and the histological malignancy grade of the 860 tumours. The classical ILC is by far the most common type, accounting for 83% of the pure lobular carcinomas, the non-classical accounts for 12%, and the mixed type only 5%. The figures are similar regarding the ILC/non-ILC. Most of the tumours are grade II.

Figure 1 shows the histological grade according to type. The pure ILC and ILC/non-ILC are shown in combination. Most of the classical ILC, 543 (78%), is grade II. This is not surprising considering the grading method and tumour morphology. The classical ILC consists of rather small tumour cells, growing in single filing without tubule formation. The number of mitoses is limited, which leaves the nuclear pleomorphism as the determining factor.

Table I. Evaluated diagnosis in 958 patients.

Pure ILC	707	(74%)
ILC/non-ILC	153	(16%)
Non-ILC	98	(10%)

Table II. Histological type and grade in 860 tumours.

No. (col.%)	Pure ILC 707	ILC/non-ILC 153
Histological type		
Classic ILC	588 (83)	113 (74)
Non-classic ILC	83 (12)	19 (12)
Mixed type	33 (5)	11 (7)
Unknown	3 (0)	10 (7)
Grade		
I	144 (20)	33 (22)
II	520 (74)	109 (71)
III	39 (6)	10 (7)
Unknown	4 (1)	1 (1)

The four (<1%) grade III tumours in this group were tumours with a high mitotic count. In contrast, the non-classic group shows a much higher proportion of grade III tumours, 39 (38%). These tumours are typically of the pleomorphic and solid variants. The growth pattern in these tumours is without tubule formation, the nuclear pleomorphism is moderate to severe and they often have a high mitotic count. The grade I tumours in this group of non-classical ILC are often of the tubulo-lobular variant.

Table III shows the distribution of the histological subtypes in the non-classical and mixed type of tumours. The pleomorphic, solid and mixed variants are the most frequent, while the alveolar and the signet-ring cell types are rare. The distribution of the histological subtypes is similar when comparing pure ILC and ILC/non-ILC.

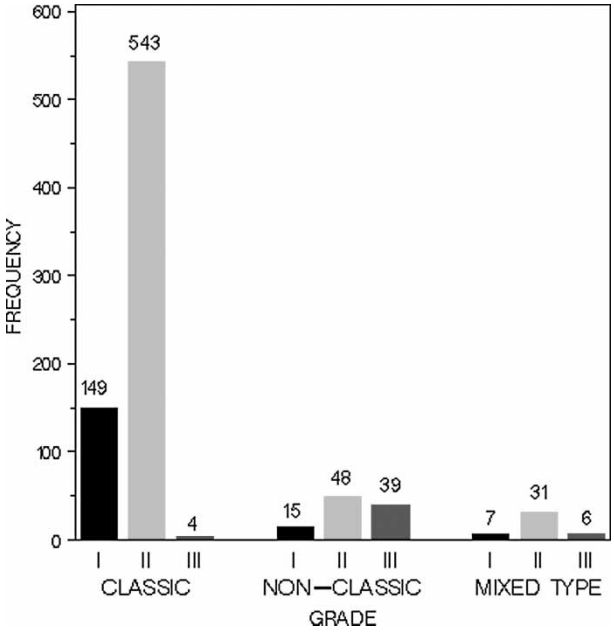

Figure 1. Distribution of histological grade according to type of lobular carcinoma.

Table III. Histological subtype in 146 patients with pure ILC or ILC/non-ILC.

No. (col.%)	Pure ILC 116	ILC/non-ILC 30
Histological subtype		
Solid	20 (17)	1 (3)
Tubulo-lobular	12 (10)	1 (3)
Pleomorphic	39 (34)	10 (33)
Signet-ring cell	4 (3)	4 (13)
Alveolar	7 (6)	3 (10)
Mixed	33 (28)	11 (37)
Unknown	1 (1)	0 (0)

Table IV shows the known prognostic factors; tumour size, axillary lymph node status and hormone receptor status, correlated to tumour grade and type, respectively. Here, the pure ILC and ILC/non-ILC are shown in combination, because the distribution is similar in the two groups. The median age is 59, (range 30–74). There is neither significant correlation between age and grade, nor between age and type. Also there is no significant correlation between tumour size and type. However, there is statistical significant correlation between tumour increase of size and grade ($p < 0.01$). Regarding lymph node status, there is a tendency towards more frequent 4+ positive lymph nodes in the non-classical ILC ($p = 0.05$). If lymph node status is compared to grade, there is a statistical significant correlation, showing increased number of positive lymph nodes among the grade III tumours ($p < 0.01$).

The data show that the ILC predominantly is a hormone receptor positive tumour, regardless of type. However, there is statistically significant correlation between hormone receptor status and grade, with increased incidence of receptor negative tumours among grade III ($p < 0.01$).

Eighteen percent of the 860 tumours showed multifocality. There is no difference regarding multifocality between the pure ILC and the ILC/non-ILC. In the group of pure ILC the frequency of carcinoma in situ was 68% and 13% regarding LCIS and ductal carcinoma in situ (DCIS), respectively. The corresponding figures in ILC/non-ILC group were 64% and 68%, respectively, and the difference in the presence of DCIS between the two groups is statistically significant ($p < 0.01$). These tumours also showed a higher frequency of vascular invasion (20%) than the pure ILC (8%), a discovery that is also statistically significant ($p < 0.01$).

Figure 2A shows disease-free survival, and 2B overall survival between the histological grades I, II and III tumours, pooling the histological types. The median estimated potential follow up is 7 years regarding disease-free survival and 9 years 11 months regarding overall survival. On disease-free survival there is a borderline difference between grade I and grade II tumours ($p = 0.05$), favouring grade I. In regards to overall survival there is no statistical significant difference ($p = 0.29$). The grade III tumours, however, have a statistically significant worse prognosis compared to grade II tumours ($p < 0.01$) regarding both disease-free survival and overall survival.

In a multivariate analysis adjusting for, tumour size, axillary lymph node status, hormone receptor status and age, we find no difference in prognosis between grade I and II tumours, but we confirm the significant difference in prognosis between grade II and III. Table V shows that the adjusted relative risk for disease-free survival is 2.30 (95% CI; 1.52–3.47) and for overall survival 2.64 (95% CI; 1.80–3.88) for grade III tumours compared to grade II tumours. Histological type is no independent prognostic factor, when adjusting for grade. There is no

Table IV. Prognostic factors in the 860 patients.

	Grade				Type			
No. (col.%)	I 177	II 629	III 49	Unknown 5	Classic 701	Non-classic 102	Mixed type 44	Unknown 13
Tumor size								
0–20 mm	120 (68)	338 (54)	20 (41)		392 (56)	51 (50)	29 (66)	
21–50 mm	43 (24)	239 (38)	20 (41)		248 (35)	42 (41)	9 (20)	
>50 mm	9 (5)	45 (7)	9 (18)		48 (7)	9 (9)	6 (14)	
Unknown	5 (3)	7 (1)	0 (0)		13 (2)	0 (0)	0 (0)	
Lymph nodes								
Negative	110 (62)	355 (56)	24 (49)		406 (58)	57 (56)	23 (52)	
1–3 positive	43 (24)	167 (27)	7 (14)		179 (26)	18 (18)	15 (34)	
>3 positive	24 (14)	107 (17)	18 (37)		116 (17)	27 (26)	6 (14)	
Hormone receptor								
Positive	146 (82)	580 (92)	39 (80)		634 (90)	89 (87)	35 (80)	
Negative	17 (10)	30 (5)	8 (16)		38 (5)	11 (11)	4 (9)	
Unknown	14 (8)	19 (3)	2 (4)		29 (4)	2 (2)	5 (11)	

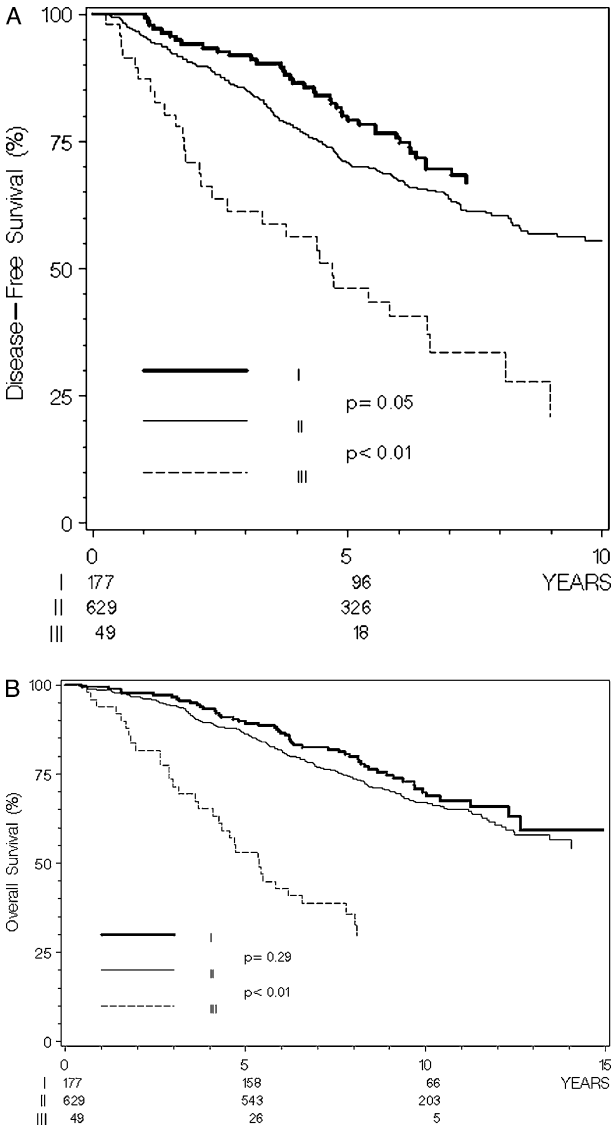

Figure 2. Disease-free survival (A) and overall survival (B) according to histological grade in lobular carcinoma. Patients at risk at 0, 5 and 10 years are given below.

interaction between histological type and grade, meaning that the relative risk of grade is the same within the different histological types. There is no difference in the significance of grade regarding pure ILC and ILC/non-ILC, i.e. no interaction is found for these parameters.

However, the number of patients enrolled in the study having a grade III tumour as a single high risk factor is very small. Only 16 of the 860 patients (2%) fall into this category, with tumour size <20 mm, hormone receptor positive tumour, and no lymph node metastasis.

Discussion

The invasive lobular carcinoma is the second most common type of breast cancer reported to the Danish Breast Cancer Cooperative Group [19]. This study shows that the incidence is rising, due to an overall increase in the incidence of breast cancer, and also due to increased knowledge of the different histological subtypes, resulting in more accurate diagnosis. At present, the histological malignancy grade has no influence on treatment strategy. In our study, most classical invasive lobular carcinoma turned out to be grade II tumours, with a minor portion being grade I and only very few grade III tumours. This was to be expected, considering the grading method (tubule formation, number of mitoses and nuclear pleomorphism) and it correlates well with the findings in other studies [17,22,23]. However, the distribution within the group of non-classical lobular carcinomas is different. Here, we found a much higher frequency of grade III tumours, mainly among the solid and pleomorphic subtypes. Several studies have shown that the prognosis of ILC varies among the different histological subtypes [3,9–11,15,16], and some studies show a correlation

Table V. Univariate non-adjusted and multivariate adjusted hazard ratios according to grade.

	Unadjusted		Adjusted	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
End-point				
Overall Survival				
Grade				
I	0.85 (0.63–1.15)	0.29	1.00 (0.73–1.37)	0.99
II	1 (reference)		1 (reference)	
III	3.42 (2.36–4.94)	<0.01	2.64 (1.80–3.88)	<0.01
Disease-free Survival				
Grade				
I	0.71 (0.50–1.00)	0.05	0.73 (0.52–1.04)	0.08
II	1 (reference)		1 (reference)	
III	2.50 (1.69–3.70)	<0.01	2.30 (1.52–3.47)	<0.01

between prognosis and histological malignancy grade in multivariate analysis [17,23]. A study by Sinha et al. including 106 cases of ILC showed no significant difference in recurrence-free survival between ILC grades I and II [22]. The proportion of ILC grade III was only 6%, and therefore no comparison with grade I was made. We also found no significant difference in prognosis between grade I and II tumours. Our material included 860 lobular carcinomas and we found a significantly worse prognosis for the grade III tumours compared to the grade II tumours, regarding both disease-free survival and overall survival, in a multivariate analysis. Since most of these grade III tumours were found among the solid and pleomorphic subtypes, the data can explain the findings in other studies showing a worse prognosis in these variants [3,9–11,15,16]. The Nottingham group showed that histological malignancy grade is the most important factor in predicting prognosis, and when combined with tumour type, gave the most accurately predicted prognosis [17]. Histological malignancy grading of ILC is not very common, probably due to a weakness of the grading method in these types of carcinomas, where the nuclear pleomorphism often is the determining factor. Our investigation supports the findings in the Nottingham study [17], showing that the grading method is a powerful prognostic indicator.

The literature regarding the reproducibility of the diagnosis of invasive lobular carcinoma is limited, with only a few studies mainly concerning the classical and pleomorphic subtypes. The reported kappa values differ, depending on the pathologists experience in breast pathology [24]. In our study most of the tumours were evaluated by one pathologist, we do not regard this as a disadvantage.

The DBCG guidelines 2004 do not recommend adjuvant treatment of ILC grade III [19]. The poor prognosis in this small group of patients, however, suggests changing the recommendations. In the Danish population the number of these patients is 6–7 per 2.700 (0.3%) enrolled patients in the DBCG protocols per year.

The rate of LCIS varies in the literature between 40% and 80% [3,6,9,15]. Martinez and Azzopardi reported a rate of LCIS of 80% and a rate of DCIS of 10% [6]. We found LCIS in 67% and DCIS in 23% of the tumours, with a significant higher portion of the latter in the ILC/non-ILC tumours ($p < 0.01$).

The invasive lobular carcinoma is mostly hormone receptor positive [22,23]. This is also the result in our study. We found a significantly lower amount of hormone receptor positive tumours among the high grade lobular carcinomas, a result supported by Mohammed et al. [25]. We also discovered correlation between histological malignancy grade and tumour size, showing increasing tumour size with increasing grade, but could not confirm the mitotic count as the determining feature as shown in a study by Bane et al. which included 50 classical ILC [23]. We found an increased number of lymph node metastases among the grade III tumours, but we did not investigate tumour stage, a function of tumour size and number of lymph node metastases, as Bane et al. did in their study [23]. Their work confirms the correlation between histological malignancy grade and tumour size. They also found increasing tumour stage, with increasing tumour grade [23].

This study shows that the incidence of ILC is increasing in Denmark, as well as other types of invasive breast carcinomas. The planned extension of organized mammography screening to include the whole country within the year 2007 is therefore important, and will improve the management of breast cancer.

In conclusion, histological malignancy grade is a valuable prognostic factor regarding invasive lobular carcinoma, and it is to some extent, associated with the histological subtype. The results in the present study suggest that histologic grade should be taken into consideration, when planning the postoperative treatment in this group of breast cancer patients.

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