

Lobular and non-lobular breast cancers differ regarding axillary lymph node metastasis: a cross-sectional study on 4,292 consecutive patients

T. Vandorpe · A. Smeets · B. Van Calster · K. Van Hoorde · K. Leunen · F. Amant · Ph. Moerman · K. Deraedt · O. Brouckaert · S. Van Huffel · H. Wildiers · M. R. Christiaens · P. Neven

Received: 28 April 2011 / Accepted: 28 April 2011 / Published online: 12 May 2011
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Abstract Invasive lobular carcinoma (ILC) accounts for 8–14% of all breast cancers and carries distinct prognostic and biologic implications. The goal of our study was to investigate the impact of lobular histology on axillary lymph node (ALN) involvement. This is a cross-sectional study of 4,292 consecutive patients surgically treated for breast carcinoma at the University Hospitals Leuven. Logistic regression analysis was used to relate ILC to lymph node involvement while controlling for the following clinicopathologic features: tumor size, multifocal disease, tumor grade, lobular subtype and the combined steroid, and Her-2 status. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed. A subgroup analysis was performed for patients that underwent a

sentinel lymph node (SLN) procedure. The observed incidence of ILC was 13%. ILCs were larger, were more often grade II, multifocal, steroid receptor positive and Her-2 negative, and tended to be present in older patients. Incidence of ALN involvement was 42.0% for ILCs versus 38.3% for other tumors (OR 1.17, 95% CI 0.97–1.40). For the SLN subgroup, ILCs were less often ALN positive than non-ILCs (20.5% versus 28.3%, OR 0.66, 95% CI: 0.41–1.00). In the multivariable analysis, the lobular subtype was identified as less likely to have ALN involvement (adjusted OR 0.66, 95% CI 0.53–0.82). The analysis for the SLN subgroup showed comparable results (adjusted OR 0.49, 95% CI 0.30–0.78). This study has demonstrated that the lobular subtype is an independent predictor of lymph node involvement with ILC having a lower incidence of involved lymph nodes. The mildly higher incidence of ALN metastasis in lobular cancers in univariable analysis is not due to the lobular subtype, but due to confounding factors that interact with lymph node involvement.

T. Vandorpe and A. Smeets contributed equally in this study.

T. Vandorpe · A. Smeets (✉) · K. Leunen · F. Amant · Ph. Moerman · K. Deraedt · H. Wildiers · M. R. Christiaens · P. Neven
Multidisciplinary Breast Centre, University Hospitals Leuven, Leuven, Belgium
e-mail: ann.smeets@uzleuven.be

T. Vandorpe · B. Van Calster · K. Van Hoorde · S. Van Huffel
Department of Electrical Engineering (ESAT-SISTA),
Katholieke Universiteit Leuven, Leuven, Belgium

B. Van Calster · K. Van Hoorde · S. Van Huffel
IBBT/K.U. Leuven Future Health Department, Katholieke
Universiteit Leuven, Leuven, Belgium

K. Leunen · F. Amant · O. Brouckaert · P. Neven
Division of Gynecologic Oncology, University Hospitals
Leuven, Leuven, Belgium

Ph. Moerman · K. Deraedt
Department of Pathology, University Hospitals Leuven, Leuven,
Belgium

Keywords Invasive lobular carcinoma · Breast cancer · Lymph node

Introduction

Lymph node involvement is the most important prognostic factor in breast cancer. It is a multifactorial event determined by tumor and patient characteristics. Variables associated with lymph node metastasis are tumor size, grade, lymphovascular invasion (LVI), multifocality, estrogen receptor (ER), progesterone receptor (PR), and HER-2 status [1].

Invasive lobular carcinoma (ILC) is the second most common type of invasive breast cancer after invasive

ductal carcinoma and accounts for 8–14% of all breast cancer cases [2, 3]. ILC is characterized by small, round cells which infiltrate both the stroma in an Indian file pattern and the adipose tissue without desmoplastic reaction, which makes early diagnosis challenging [2]. Absence of E-cadherin expression is considered as a characteristic of ILC [3]. The diagnosis of ILC carries distinct prognostic and biologic implications. Differences in clinical behavior between ILCs and invasive ductal carcinomas have been reported [2–7]. ILCs have a propensity for multifocal and multicentric distribution but also for bilateralism and a particular pattern of metastatic spread. The incidence of ILC is increasing, especially among postmenopausal women using hormone replacement therapy.

The goal of our study was to investigate the impact of lobular histology on lymph node involvement.

Patients and methods

Design, setting, and patients

This was a retrospective cross-sectional study based on data from patients of the Multidisciplinary Breast Centre of the University Hospitals Leuven, Belgium. This database contains data on 4,486 female patients with a primary operable invasive breast cancer from the period between 2000 and 2009. Exclusion criteria were (1) patients who had neoadjuvant systemic therapy (2) patients who never had breast cancer surgery (3) patients whose pathologic assessment was not performed in the University Hospitals Leuven (4) patients with primary metastatic disease. Of the 4,486 patients satisfying these criteria, 19 were ER negative and PR positive. We excluded these patients because there is controversy regarding such tumors. There were 175 patients (3.9% of 4,467) with missing data for one or more of the studied variables, most often due to lack of sufficient tumor tissue for correct pathologic assessment of molecular markers. These tumors were excluded for analysis, resulting in a dataset of 4,292 tumors. Patients that underwent a sentinel lymph node (SLN) procedure ($n = 1,506$) were defined as a subgroup for which a separate analysis was performed following the analysis on all patients.

Variables studied

The following variables were examined: age at diagnosis, maximal microscopic tumor size (largest diameter), histology (ILC vs. non-ILC), worst tumor grade, multifocal disease, axillary lymph node (ALN) status, and the combined ER, PR, and HER-2/*neu* status. Histology and multifocal disease were analyzed as dichotomous variables, the combined receptor status as six-level categorical.

Determination of tumor grading and ER, PR, and HER-2/*neu* status was done according to established procedures, which have been described in more detail elsewhere [8]. A breast cancer was allocated to the lobular subtype if more than 90% of the tumor mass harbored morphological features of the lobular type; this was always confirmed by lack of E-cadherin expression. Tumors with mixed ductal and lobular phenotype were considered as non-ILC. Tumors with a lobular growth pattern with an E-cadherin-positive phenotype were classified as non-ILCs. In case of multifocal disease, the largest tumor was used for size and histotype. In case of bilateral breast cancer, both sides were included as separate tumors.

Lymph nodes in an ALN dissection were examined by H&E staining using three sections per node; according to published guidelines, lymph nodes from lobular breast cancers classified as lymph node negative on H&E were additionally stained with epithelial markers. SLN was routinely examined by serial sectioning and IHC. Isolated tumor cells were classified as lymph node negative.

Statistical analysis

First, ILC and non-ILC tumors are compared with respect to grade, combined receptor status, multifocality, age at diagnosis, and tumor size. Kendall's tau test was used for tumor grade, the Mann–Whitney test (i.e., Wilcoxon rank sum) for age and tumor size, and likelihood ratio chi-square tests for the categorical variables. Then, univariable relationships with ALN are investigated using odds ratios (ORs) with 95% CIs. Finally, a multivariable logistic regression model is constructed to assess the independent relationships with ALN using adjusted OR and 95% CIs. Covariates included in the multivariable analysis were age, tumor size, multifocal disease, tumor grade, and the combined ER, PR, and Her-2 status. Linearity for the continuous predictor variables (age, tumor size and tumor grade) was investigated using generalized additive models based on smoothing splines [9]. Goodness-of-fit was assessed using calibration plots that indicate the accuracy of the estimated probabilities of ALN involvement. All analyses were performed using Design package in R version 2.8.1 (www.r-project.org) and using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Univariable analysis

The incidence of ILC observed in this study was 13%. Table 1 summarizes the patients and tumor characteristics according to the histologic subtype. There were several apparent differences in tumor characteristics between ILCs

Table 1 Patient and tumor characteristics according to the histologic subtype

Variable	Statistic	ILC	Non-ILC	<i>P</i>
Grade				
1	<i>N</i> (col %)	7 (1.3)	633 (17.0)	<0.001 ^a
2	<i>N</i> (col %)	476 (85.5)	1,445 (38.7)	
3	<i>N</i> (col %)	74 (13.3)	1,657 (44.4)	
ER, PR, HER-2				
ER–, PR–, Her-2–	<i>N</i> (col %)	7 (1.3)	419 (11.2)	<0.001
ER–, PR–, Her-2+	<i>N</i> (col %)	4 (0.7)	181 (4.9)	
ER+, PR–, Her-2–	<i>N</i> (col %)	56 (10.1)	347 (9.3)	
ER+, PR–, Her-2+	<i>N</i> (col %)	2 (0.4)	89 (2.4)	
ER+, PR+, Her-2–	<i>N</i> (col %)	475 (85.3)	2,502 (67.0)	
ER+, PR+, Her-2+	<i>N</i> (col %)	13 (2.3)	197 (5.3)	
Multifocality	<i>N</i> (col %)	88 (15.8)	374 (10.0)	<0.001
Age (years)	Median (IQR)	59 (50–68)	57 (49–67)	0.001 ^b
Tumor size (mm)	Median (IQR)	30 (17–50)	20 (14–30)	<0.001 ^b

^a Kendall's tau test^b Wilcoxon rank sum test

and non-ILCs. ILCs were more often grade II, had larger tumor sizes, were more often multifocal, tended to be present in older patients, and are more frequently ER+/PR+/Her-2–.

The results of the univariable prediction of ALN involvement are shown in Table 2. ILCs were slightly more likely to have ALN involvement compared to non-ILCs (42.0% vs. 38.3%; OR = 1.17; 95% CI: 0.97–1.40). The overall frequency of lymph node metastasis was 39%. The following factors were univariably related to a higher

probability of lymph node involvement: high tumor grade, larger tumor size, multifocal disease, and a ER–/PR–/Her-2+ or ER+/PR+/Her-2+ profiles. No strong effect of age at breast cancer diagnosis on ALN involvement was observed.

The univariable analyses were repeated for the subgroup of 1,506 patients that underwent a SLN biopsy, as shown in Table 3. In this subgroup analysis, ILCs were less likely ALN positive than non-ILCs (20.5% vs. 28.3%; OR = 0.65, 95% CI: 0.41–1.00). The tumor diameter in

Table 2 Univariable prediction of ALN involvement

Variable	Statistic	LN+	LN–	OR of LN+ (95% CI)	<i>P</i>
Histology					
ILC	<i>N</i> (row %)	234 (42.0)	323 (58.0)	ILC vs. non-ILC: 1.17 (0.97–1.40)	0.093
Non-ILC	<i>N</i> (row %)	1,430 (38.3)	2,305 (61.7)		
Grade					
1	<i>N</i> (row %)	161 (25.2)	479 (74.8)	Vs. grade 1: 1.78 (1.46–2.19) 2.46 (2.01–3.01)	<0.001
2	<i>N</i> (row %)	720 (37.5)	1,201 (62.5)		
3	<i>N</i> (row %)	783 (45.2)	948 (54.8)		
ER, PR, HER-2					
ER–, PR–, Her-2–	<i>N</i> (row %)	148 (34.7)	278 (65.3)	Vs. ER– PR– Her-2–: 1.63 (1.15–2.32) 1.10 (0.83–1.46) 1.12 (0.70–1.78) 1.17 (0.95–1.46) 1.77 (1.27–2.49)	0.005
ER–, PR–, Her-2+	<i>N</i> (row %)	86 (46.5)	99 (53.5)		
ER+ PR– Her-2–	<i>N</i> (row %)	149 (37.0)	254 (63.0)		
ER+, PR–, Her-2+	<i>N</i> (row %)	34 (37.0)	57 (63.0)		
ER+, PR+, Her-2–	<i>N</i> (row %)	1,145 (38.5)	1,832 (61.5)		
ER+, PR+, Her-2+	<i>N</i> (row %)	102 (48.6)	108 (51.4)		
Multifocal					
Unifocal	<i>N</i> (row %)	1,448 (37.8)	2,382 (62.2)	Multi- vs. unifocal: 1.44 (1.19–1.75)	<0.001
Multifocal	<i>N</i> (row %)	216 (46.8)	246 (53.3)		
Age	Median (IQR)	56 (48–66)	58 (49–67)	0.97 per 10 year (0.92–1.02)	0.174
Tumor size (mm)	Median (IQR)	30 (20–45)	19 (12–26)	1.52 per cm (1.46–1.59)	<0.001

Table 3 Univariable prediction of ALN involvement for SLN patients only

Variable	Statistic	LN+	LN–	OR of LN+ (95% CI)	<i>P</i>
Histology					
ILC	<i>N</i> (row %)	27 (20.5)	105 (79.5)	ILC vs. non-ILC: 0.65 (0.41–1.00)	0.056
Non-ILC	<i>N</i> (row %)	389 (28.3)	985 (71.7)		
Grade					
1	<i>N</i> (row %)	81 (25.4)	238 (74.6)	Vs. grade 1: 1.11 (0.82–1.50) 1.23 (0.90–1.70)	0.429
2	<i>N</i> (row %)	191 (27.3)	508 (72.7)		
3	<i>N</i> (row %)	144 (29.5)	344 (70.5)		
ER, PR, HER-2					
ER–, PR–, Her-2–	<i>N</i> (row %)	27 (20.5)	105 (79.6)	Vs. ER– PR– Her-2–: 1.62 (0.67–3.73) 1.55 (0.88–2.75) 0.71 (0.20–2.04) 1.57 (1.02–2.48) 1.57 (0.79–3.10)	0.309
ER–, PR–, Her-2+	<i>N</i> (row %)	10 (29.4)	24 (70.6)		
ER+, PR–, Her-2–	<i>N</i> (row %)	36 (27.7)	94 (72.3)		
ER+, PR–, Her-2+	<i>N</i> (row %)	4 (15.4)	22 (84.6)		
ER+, PR+, Her-2–	<i>N</i> (row %)	320 (28.6)	798 (71.4)		
ER+, PR+, Her-2+	<i>N</i> (row %)	19 (28.8)	47 (71.2)		
Multifocal					
Unifocal	<i>N</i> (row %)	380 (27.1)	1,020 (72.9)	Multi- vs. unifocal: 1.38 (0.90–2.09)	0.131
Multifocal	<i>N</i> (row %)	36 (34.0)	70 (66.0)		
Age	Median (IQR)	57 (50–65)	57 (49–66)	1.02 per 10 year (0.92–1.12)	0.656
Tumor size (mm)	Median (IQR)	20 (15–25)	15 (10–20)	1.53 per cm (1.37–1.72)	<0.001

the SLN subgroup was significantly smaller than in the non-SLN group with a median tumor size of 17 mm versus 25 mm, respectively ($P < 0.001$). Apart from the obvious loss in statistical power, the univariable ORs of age at diagnosis, tumor size, and multifocal disease were comparable to those obtained on all patients. The effect of grade was weaker. The effect of combined receptor status was difficult to compare given the large number of small counts for the SLN subgroup (Table 3).

Multivariable logistic regression

Multivariable analyses were performed using a logistic regression model to determine whether ILC is an independent predictive factor for lymph node involvement.

The results of the regression model and corresponding adjusted ORs are presented in Table 4. The multivariable model identified the lobular subtype as less likely to have ALN involvement. The OR for ILCs versus non-ILCs is 0.66 (95% CI: 0.53–0.82) in the multivariable model. The predicted risks of ALN involvement for ILC and non-ILC tumors are illustrated in Fig. 1. The plot shows the risk by tumor size while fixing the other covariates at their overall median values: grade 2, unifocal, ER+/PR+/Her-2– tumors for patients who were 58-year old at diagnosis. The plot clearly illustrates that ILC tumors have a smaller chance of ALN involvement.

Multivariable analysis of the subgroup that underwent a SLN procedure confirms the significant lower probability

of ALN involvement in ILC tumors as well (OR = 0.49; 95% CI: 0.30–0.78). The results are presented in Table 4.

Discussion

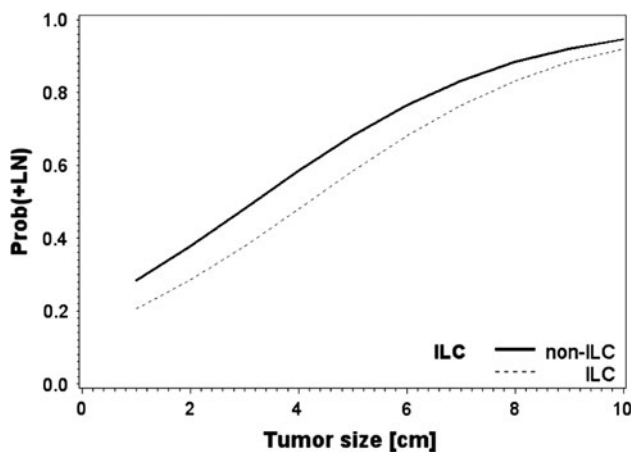
The incidence of ILCs observed in our series of 4,292 breast tumors (13%) is in accordance with the incidence range of 8–14% reported in the literature [2].

Largely in agreement with other series, patient and tumor characteristics at diagnosis are different for ILC than for non-ILC [2–4, 6, 7, 10]. ILCs are larger at diagnosis, more often grade II, more often multifocal, are frequently ER+, PR+, Her-2–, and tend to present in older patients (Table 1). A lower proliferative rate and the lack of a desmoplastic reaction may make ILC impalpable or invisible, explaining why ILC tends to present at older age and as a larger tumor than non-ILCs [3].

We observed more ALN involvement in ILC tumors compared to non-ILC tumors (42.0% vs. 38.3%). Prior series comparing lobular and non-lobular tumors are not consistent regarding the incidence of lymph node involvement in lobular tumors. The largest published series including 263,408 patients from SEER database are in line with our results while a large series from Bayer College including 4,140 ILCs and 45,169 IDCs showed no difference in the incidence of lymph node involvement between both groups. Sastre even found a lower incidence of involved lymph nodes in lobular tumors.

Table 4 Multivariable logistic regression predicting ALN involvement for all patients and for the SLN patients separately

Variable	All patients			SLN subgroup		
	Coefficient	OR (95% CI)	P	Coefficient	OR (95% CI)	P
ILC	-0.421	0.66 (0.53–0.82)	<0.001	-0.722	0.49 (0.30–0.78)	0.003
Grade						
1	Reference level			Reference level		
2	0.314	1.37 (1.10–1.71)	<0.001	0.091	1.10 (0.80–1.51)	0.714
3	0.550	1.72 (1.38–2.18)		0.151	1.16 (0.81–1.67)	
ER, PR, HER-2						
ER–, PR–, Her-2–	Reference level		0.005	Reference level		0.183
ER–, PR–, Her-2+	0.436	1.55 (1.06–2.25)		0.516	1.68 (0.67–3.98)	
ER+, PR–, Her-2–	0.350	1.42 (1.04–1.94)		0.557	1.75 (0.95–3.23)	
ER+, PR–, Her-2+	0.219	1.25 (0.76–2.03)		-0.313	0.73 (0.20–2.15)	
ER+, PR+, Her-2–	0.415	1.51 (1.19–1.93)		0.571	1.77 (1.10–2.92)	
ER+, PR+, Her-2+	0.669	1.95 (1.37–2.79)		0.609	1.84 (0.91–3.69)	
Multifocality	0.466	1.60 (1.30–1.96)	<0.001	0.372	1.45 (0.93–2.24)	0.097
Age	-0.003	0.97 per 10 year (0.92–1.02)	0.206	0.003	1.03 per 10 year (0.93–1.14)	0.604
Tumor size (cm)	0.422	1.53 per cm (1.46–1.60)	<0.001	0.433	1.54 per cm (1.37–1.73)	<0.001

**Fig. 1** Multivariable logistic regression: probability of ALN involvement versus tumor size. *Full* and *dashed* plot lines are model predictions for, respectively, non-ILC and ILC tumors with the following fixed characteristics: grade II, unifocal, ER+, PR+, and HER-2– for age 58

In the univariable prediction of ALN involvement in our series, tumor size, multifocality, grade, and the molecular markers were significant predictors for lymph node involvement. In contrast, age and lobular histology were not significantly correlated with lymph node involvement in our series.

In the published studies that address the predictors for ALN metastasis in the pre-SLN and SLN eras, tumor size, age, LVI, and histologic subtype were the variables most commonly described as independently associated with ALN involvement. In SLN studies, the variables associated with SLN metastases were, as expected, quite similar [6, 11, 12].

To evaluate whether the higher incidence of ALN involvement in lobular tumors is a consequence of the lobular histology or of other covariates that interact with ALN involvement, we built a multivariable model correcting for age, tumor size, tumor grade, multifocality, and the combined ER, PR, and Her-2 status. All these covariables differed between lobular and non-lobular tumors and correlated with lymph node involvement. The multivariable logistic regression showed a significantly lower incidence of involved lymph nodes in ILCs compared to non-ILCs (OR = 0.66; 95% CI: 0.53–0.82).

Prior multivariable analyses are not consistent regarding ILC as an independent predictor for lymph node involvement. In the bulk of the literature, the lobular subtype is not an independent predictor for lymph node involvement [11, 13–16]. It is important to keep in mind that most of these studies only included patients eligible for the SLN procedure (clinical node negative, smaller tumors, and unifocal). A lower probability of ALN metastasis for ILC against ductal was shown by Viale in a large series of 4,351 patients although not significant (OR = 0.84; 95% CI: 0.65–1.07).

There can be several reasons why ILCs might be less likely ALN positive than non-ILCs.

First, the uniform appearance of bland tumor cells that lack cellular atypia and often have a low mitotic rate makes the lobular carcinoma cells more difficult to detect in metastatic lymph nodes [17]. The reported higher rate of false-negative lymph nodes by histologic examination in lobular carcinomas could cause a general under-staging of the histologic type at the time of surgery. In our series, IHC was used to assess ALN of all lobular tumors when routine

H&E was negative. While contribution of IHC over H&E to improve lymph nodal staging in ILC remains controversial [18, 19], one could assume the possibility of a higher false-negative rate in the non-ILC group since IHC was not performed in these cases. Therefore, we might even be underestimating differences in ALN involvement between ILC and non-ILC.

In the subgroup analysis of patients that underwent a sentinel procedure, however, all SLNs, ILC, and non-ILC were examined by enhanced pathology (serial sectioning and immunohistochemistry), reducing the chance of underestimating the differences in lymph node involvement due to different pathological assessments. In this subgroup analysis, patients with a lobular tumor were less likely to be lymph node positive, strengthening our finding that the higher incidence of lymph node involvement in lobular tumors in univariable analysis might be due to confounding variables such as tumor size and occurrence of multifocal disease rather than the lobular subtype as such. This idea is supported by the fact that in the sentinel subanalysis, an inherently and at least partially stratified subgroup concerning tumor size (as mainly small tumors are included for the SLN procedure), SLN involvement is lower in ILC than in non-ILC (20.5 and 28.3%, respectively, OR 0.66, 95% CI: 0.41–1.00). According to the literature, tumor size seems by far the most powerful predictor of ALN involvement [1, 6, 20, 21], but histology (ILC vs. non-ILC) is at least as important in our multivariate ALN/SLN model as independent prognostic factor (Table 4).

Second, genes involved in the metastatic process of ILCs might be different from those involved in non-ILC. Yoder stated that ILCs are thought to arise from the same cell type as infiltrating ductal carcinoma with distinct genomic changes resulting in a different phenotype. Based on these genetic findings, loss of E-cadherin has become a widely used IHC parameter to diagnose ILCs. All our ILC cases were confirmed E-cadherin negative. However, retention of E-cadherin in ILC is rare, and loss of E-cadherin in non-ILCs has been described in 7.2% of non-ILCs [22, 23] without an impact on ALN status and therefore unlikely to affect our results.

Third, ALN involvement may be a function of tumor volume/surface area rather than tumor diameter. Theoretic models have shown that the propensity for metastases depends on the total number of cells of a tumor combined with the probability of each individual cell to disseminate [24]. As tumors of similar diameter are different three-dimensional objects, the number of cells might be better estimated by three-dimensional parameters such as tumor volume than by a linear measurement. Tumor volume or cell load and even microvessel density may differ between ILCs and non-ILCs. Recent data do not support the

assumption that three-dimensional measurements have an improved prognostic capability in comparison with traditional one-dimensional measurements. Lobular carcinomas, however, were excluded from analysis because in many cases, there is no grossly well-demarcated mass, and, therefore, three-dimensional assessment of size is imprecise [25].

ALN is the best independent prognostic factor for disease-free and overall survival of breast cancer. Our findings of a lower likelihood for cell migration towards lymph nodes are in line with previous and more recent reports which suggested that prognosis is better for patients with ILC than for those with invasive ductal adenocarcinoma after matching for tumor stage [7, 26–28]. Both types of carcinoma are usually managed with the same adjuvant strategy which may be over-treatment for ILC as they are less systemically aggressive.

In conclusion, this study demonstrates that the lobular subtype is an independent predictor for lymph node involvement with lobular cancer having a lower incidence of involved lymph nodes. The higher incidence of lymph node metastasis in lobular cancers in univariable analysis is not due to the lobular subtype, but to confounding factors that interact with lymph node involvement.

Acknowledgments BVC is a postdoctoral fellow of the Research Foundation—Flanders (FWO). KVH is supported by a grant from the Agency for Innovation by Science and Technology (IWT).

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