Management of the axilla in breast cancer: outcome analysis in a series of ductal versus lobular invasive cancers

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Abstract

Introduction Axillary lymph node dissection (ALND) has been considered essential for the staging of breast cancer (BC). As the impact of tumor biology on clinical outcomes is recognized, a surgical de-escalation approach is being implemented. We performed a retrospective study focused on surgical management of the axilla in invasive lobular carcinoma (ILC) versus invasive ductal carcinoma (IDC).

Materials and methods 1151 newly diagnosed BCs, IDCs (79.6%) or ILCs (20.4%), were selected among patients treated at our Breast Cancer Unit from 2012 to 2018. Tumor characteristics and clinical information were collected and predictors of further metastasis after positive sentinel lymph node biopsy (SLNB) analyzed in relation to disease-free survival (DFS) and overall survival (OS).

Results 27.5% of patients with ILC had ≥ 3 metastatic lymph nodes at ALND after positive SLNB versus 11.48% of IDCs ($p = 0.04$). Risk predictors of further metastasis at ALND were the presence of > 2 positive lymph nodes at SLNB (OR = 4.72, 95% CI 1.15–19.5 $p = 0.03$), T3–T4 tumors (OR = 4.93, 95% CI 1.10–22.2, $p = 0.03$) and Non-Luminal BC (OR = 2.74, 95% CI 1.16–6.50, $p = 0.02$). The lobular histotype was not associated with the risk of further metastasis at ALND (OR = 1.62, 95% CI 0.77–3.41, $p = 0.20$).

Conclusions ILC histology is not associated with higher risk of further metastasis at ALND in our analysis. However, surgical management decisions should be taken considering tumor histotype, biology and expected sensitivity to adjuvant therapies.

Keywords Invasive lobular carcinoma · Invasive ductal carcinoma · Axilla · Surgical management · ALND · Breast cancer

Introduction

Recognition of tumor biology as the single most important factor associated with the risk of local and distant recurrence of breast cancer pushed clinicians to re-evaluate the role of surgery in disease management [1]. After de-escalation of the primary lesion's treatment, and introduction of SLNB, the surgical management of the axilla has been the subject of pivotal studies aimed at reducing extensive surgery and the ensuing complications [2].

ILCs have distinctive biological and clinical behavior, which set them apart from the other molecular subtypes, also impacting on response to adjuvant and neoadjuvant treatments and clinical outcomes [3]. Despite this, current guidelines (NCCN–ESMO 2019) do not provide individual recommendations for invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC).

We questioned whether IDCs and ILCs should be treated in the same way when it comes to loco-regional disease

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control, especially after acquisition of the latest practice-changing results from Z0011 and alike. Z0011 10-year follow-up data confirmed the non-inferiority of breast-conserving surgery (BCS) with SLNB alone versus ALND in selected patients with metastatic lymph nodes at SLNB [4]. Unfortunately, the lobular histotype was very under-represented in the study and a sub-analysis according to tumor histotype was not performed.

Here, we report results from a retrospective study focused on newly diagnosed ILC and IDC patients treated at the Breast Cancer Unit of Cattinara Teaching Hospital between 2012 and 2018.

The aim of this work was to compare the involvement of axillary lymph nodes in the two major histological breast cancer types, analyzing factors influencing the risk of further axillary metastases after positive SLNB.

Methods

Patients

Patients' data were extracted from *dataBreast*, a database used to collect and monitor diagnosis, management, treatment and follow-up of BC patients, according to EUSOMA (EUropeanSOciety of Mastology) guidelines. 1616 patients with newly diagnosed breast invasive tumors were treated in Trieste's Breast Unit between 2012 and 2018. From this cohort, we selected women with either an IDC or ILC, 1246 (77%), excluding other histotypes BCs (papillary, mucinous, etc.). Other exclusion criteria were as follows: 95 patients were not included in the analysis for metastatic carcinomas at diagnosis (20), lack of axillary assessment (33) and neo-adjuvant therapy (42). 1151 tumors, 916 (79.6%) IDCs and 235 (20.4%) ILCs, were ultimately included in the analysis (see Fig. 1). The following variables were noted for each patient: age, familiarity, surgical procedure, tumor size (pT), lymph node status (pN), TNM stage, tumor grade, estrogen (ER) and progesterone (PR) status, proliferative activity with the expression of Ki-67, human epidermal growth factor receptor 2 (Her2) status, molecular subtype, presence of angiovascular invasion, dissected SLNB number, number of positive SLNs, number of SLNB with micro- and macro-metastases, number of patients who underwent ALND, number of dissected lymph nodes during ALND and number of positive lymph nodes after ALND.

Patient treatment

Patients underwent "triple assessment": clinical examination, imaging and morphological investigations of primary lesion through Fine Needle Aspiration Cytology (FNAC) or core biopsy. Pre-operative axillary ultrasound (AUS) was performed in all patients: US-FNAC was performed only in the presence of a suspicious LN detected by AUS, and, in the case of confirmed axillary metastases, patient

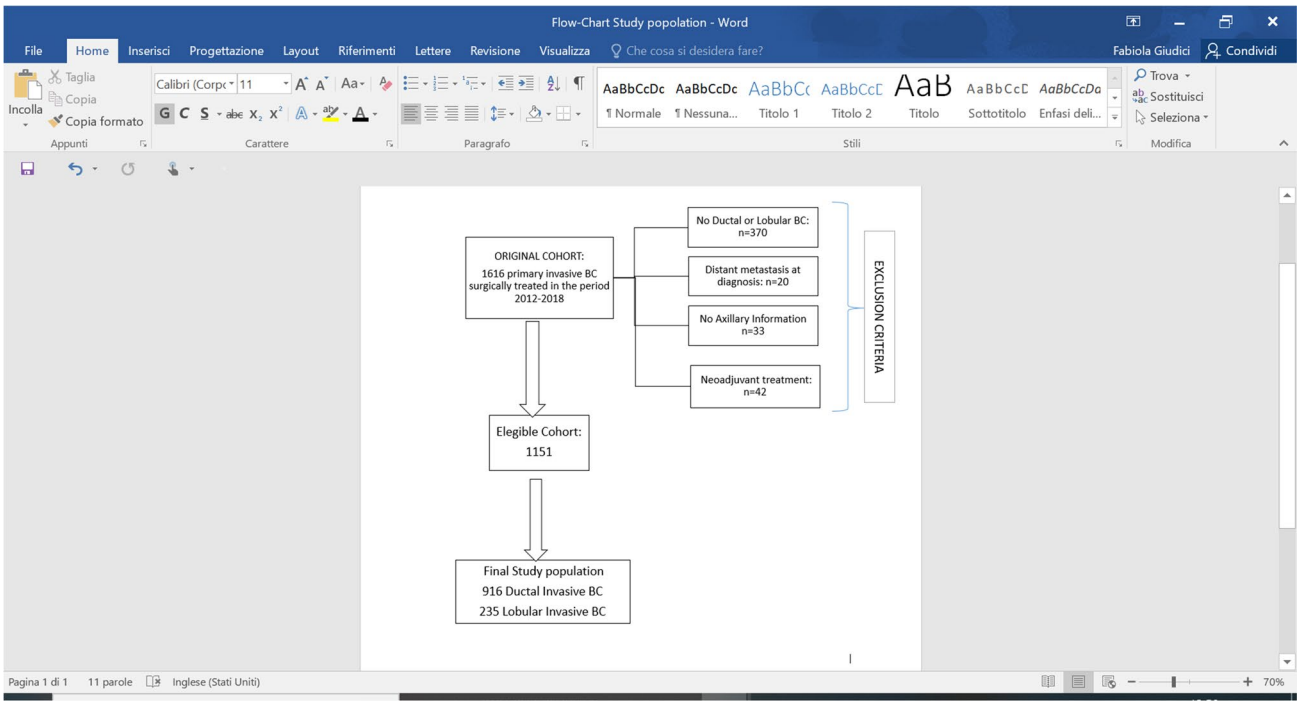

Fig. 1 Flow chart of Inclusion and Exclusion Criteria of cohort study

underwent ALND. SLNB was performed in patients with negative cytology on US-FNAC and/or unsuspicious AUS report. Primary surgery was BCS or mastectomy.

Criterion for ALND after SLNB was the presence of macrometastatic deposits (> 2.0 mm) in > 1 lymph node. If micro-metastases (i.e., deposits > 0.2 mm and < 2.0 mm) were found at SLNB, no ALND was performed.

SLN biopsy protocol and touch imprint intra-operative cytology (TIIC)

Breast cancer patients with clinically negative nodes underwent SLNB with intra-operative evaluation of the SLN(s) using touch imprint cytology (TIIC). Pre-operative lymphoscintigraphy and lymphatic mapping were performed the day before surgery. Positive SLNs were intraoperatively localized using a gamma probe and immediately sent to pathology. The SLN was cut in slices of 2–3 mm on the short axis. To obtain cellular material, some of the cut surfaces were scraped or pressed on a slide, dehydrated with alcohol solution (50–100%), stained with hematoxylin eosin and microscopically examined. The SLN was formalin-fixed and paraffin-embedded: Paraffin blocks were sectioned at 250-micron intervals. Morphologic examination was integrated with immunohistochemical analysis. Axillary lymph node dissection (ALND) was performed at the time of breast surgery (when TIIC was intensively positive) or successively after positive result at the definitive pathology. Indication for completion ALND was, till 2014, the presence of either micro- or macro-metastasis in the SLN. From 2014 till 2018, ALND was performed only in the presence of at least one macrometastatic lymph node. Through 2018 no patients were treated according to Z0011 or AMAROS criteria. We began applying these criteria from January 2019.

Statistical analysis

Patients' characteristics were summarized using descriptive and categorized analyses. Continuous data were described using mean, median, minimum and maximum values. Categorical data were expressed using absolutes frequencies and percentages. Normal variable distribution was verified with the Shapiro–Wilk test.

Comparison between IDCs and ILCs characteristics was obtained through *t* Student or the Mann–Withney test, according to the data distribution for the continuous variables and via the Chi-square or the Fisher test when appropriate, for the categorical variables.

Univariate and multivariate logistic regression analyses were used to identify predictive factors of further metastases after positive SLNB and the result expressed as odds ratio (OR), with 95% confidence interval. Statistically significant variables at 10% level at univariate analysis were selected as candidate prognostic factors for multivariate logistic regression analysis.

DFS was defined as the time from the date of surgery to the date of the first event, including local/regional disease recurrence and distant metastasis. OS was defined as the time from date of surgery to death from any cause. Last follow-up update was performed on April 30, 2019. Kaplan–Meier curves were used to visualize the survival distributions, and log-rank tests were conducted to assess the differences between two groups. The multivariable Cox proportional hazards models adjusting the confounding variables were fitted to evaluate the differences between ILC and IDC in OS and DFS, respectively, where hazard ratio (HR) with 95% confidence interval (CI) for each variable was calculated. Statistically significant variables at 10% level at univariate analysis were selected as candidate prognostic factors for multivariate Cox analysis. Moreover, since type of surgery, tumor size and lymph node status were correlated with tumor stage, we decided to exclude the evaluation of the latter in the multivariable analysis.

The R Foundation for Statistical Computing version 3.5.0 and STATA 14.2 (StataCorp, College Station, Texas) were used for the analysis. Statistical significance was expressed as $p < 0.05$.

Results

1151 patients, all women, 916 (79.6%) IDCs and 235 (20.4%) ILCs, treated at the Breast Cancer Unit—ASUITS from 2012 to 2018, were included in this analysis. 34 patients had bilateral disease.

Patients' characteristics are summarized in Tables 1, 2.

Age at diagnosis and family history were similar in the two subgroups, even though ILC was more commonly diagnosed in older patients (median age, respectively, 68 versus 65, $p = 0.014$).

Significantly higher rate of mastectomies was found in ILC patients in comparison to IDL (45.53% vs 37.12%, $p = 0.01$).

Tumor dimension and stage at diagnosis were increased in the ILC group ($p < 0.001$). Tumor grading was more equally distributed in the IDC group, while, as expected, over 88% of all ILC patients presented with a grade 2 lesion ($p < 0.001$). As it is typical of classical ILCs, vascular invasion was absent ($p < 0.001$) and Ki67 lower than 20% ($p < 0.001$) in the majority of ILCs.

85% of all patients underwent SLNB at surgery as no evidence of axillary lymph node involvement was detected clinically. 12% of all patients had a positive FNA of the axillary lymph nodes and underwent ALND. The percentage of patients who underwent ALND with or without previous SLNB was similar within the two groups: 29.91% for IDC

Table 1 Pathological and clinical characteristics in the ductal and lobular tumor histotype subgroups

	Ductal ($n=916$)	Lobular ($n=235$)	p Value
Age (Years)			
Mean ± SD	63.7 ± 12.6	62 ± 11	0.01
Median (Min–Max)	65 (24–90)	68 (39–92)	
Family history			
No	506 (55.24%)	128 (54.47%)	0.72
Yes 1° degree	127 (13.86%)	29 (12.34%)	
Yes 2° degree	188 (20.52%)	48 (20.43%)	
Unknown	95 (10.37%)	30 (12.77%)	
Surgical procedure			
Conservative surgery	576 (62.88%)	128 (54.47%)	0.02
Mastectomy	340 (37.12%)	107 (45.53%)	
Pre-operative FNAC axilla			
No	718 (78.38%)	191 (81.28%)	0.62
Yes negative	87 (9.50%)	20 (8.51%)	
Yes positive	111 (12.12%)	24 (10.21%)	
Axillary surgery			
SLNB	778 (84.93%)	200 (85.11%)	0.32
ALND after positive axillary FNAC	111 (12.12%)	24 (10.21%)	
ALND—other reasons (multicentric, cT3–4, age)	27 (2.95%)	11 (4.68%)	
Tumor Dimensions (mm)			
Mean ± SD	17.62 ± 14.98	23.68 ± 18.38	< 0.001
Median (Min–Max)	14.50 (0.20–150)	17.0 (0.25–110)	
Tumor stage			
Tmic–T1a–T1b	301 (32.86%)	43 (18.30%)	< 0.001
T1c	342 (37.34%)	92 (39.15%)	
T2	231 (25.22%)	74 (31.49%)	
T3–4	42 (4.59%)	26 (11.06%)	
Nodal Stage			
N0	599 (65.39%)	142 (60.43%)	0.23
N1mi	47 (5.13%)	18 (7.66%)	
N1a–b	183 (19.98%)	46 (19.57%)	
N2–N3	87 (9.50%)	29 (12.34%)	
TNM Stage			
I	545 (59.50%)	125 (53.19%)	0.08
II	270 (29.48%)	73 (31.06%)	
III	101 (11.03%)	37 (15.74%)	
Grading			
G1	117 (12.77%)	6 (2.55%)	< 0.001
G2	511 (55.79%)	207 (88.09%)	
G3	288 (31.44%)	22 (9.36%)	
Angiovascular invasion			
Present	248 (27.25%)	25 (10.68%)	< 0.001
Absent	662 (72.75%)	209 (89.32%)	
Ki-67			
< 20	451 (49.34%)	158 (67.81%)	< 0.001
> = 20	463 (50.66%)	75 (32.19%)	
Biological Profile			
Luminal A	395 (43.22%)	139 (59.40%)	< 0.001
Luminal B HER2-	306 (33.48%)	77 (32.91%)	

FNAC fine needle aspiration cytology; *SLNB* sentinel lymph node biopsy; *ALND* axillary lymph node dissection

Table 2 SLNB and ALND surgery data

	Ductal ($n=916$)	Lobular ($n=235$)	p Value
ALND			
Yes (first surgery or post SLNB +)	274 (29.91%)	79 (33.62%)	0.27
No	642 (70.09%)	156 (66.38%)	
ALND			
1 Operation	249 (90.88%)	64 (81.01%)	0.02
2 Operation	25 (9.12%)	15 (18.99%)	
SLNB result*			
Negative	586 (75.81%)	133 (67.78%)	0.02
Positive	187 (24.19%)	64 (32.32%) 0.02	
*Excluding 8 cases with no signal detected			
No of examined SLNB			
1	355 (45.92%)	85 (43.15%)	0.57
2	214 (27.68%)	62 (31.47%)	
> = 3	204 (26.39%)	50 (25.38%)	
No of metastatic SLNB			
1	148 (79.14%)	52 (81.25%)	0.63
2	31 (16.58%)	8 (12.50%)	
> = 3	8 (4.28%)	4 (6.25%)	
SLNB metastasis dimensions			
Micro-metastases (N1mi)	66 (35.29%)	18 (28.13%)	0.29
Macro-metastases (N1–2–3)	121 (64.71%)	46 (71.87%)	
No of removed lymph nodes at ALND			
Average ± SD	19.22 ± 7.18	17.55 ± 7.81	0.03
Median (Min–Max)	18 (9–51)	15 (9–60)	
ALND results after positive SLNB			
Negative LN	77 (63.11%)	19 (47.50)	0.07
Positive LN	45 (36.89%)	21 (52.50%)	
No of positive LN removed at ALND after positive SLNB			
0	77 (63.11%)	19 (47.50%)	0.04
1–2	31 (25.41%)	10 (25.00%)	
> = 3	14 (11.48%)	11 (75.50%)	
Extracapsular extension			
Yes	129 (17.62%)	37 (20.22%)	0.42
No	603 (82.38%)	146 (79.78%)	

SLNB sentinel lymph node biopsy; *ALND* axillary lymph node dissection; *FNAC* fine needle aspiration cytology

patients versus 33.62% for ILC patients; however, a higher number of patients received ALND after SLNB in the ILC group (18.99% ILCs versus 9.12% IDCs, $p=0.015$). SLNB was positive for tumor metastases in 32.32% of ILC patients versus 24.19% of IDCs ($p=0.023$). Moreover, almost double the number of patients with lobular histology underwent ALND at first surgery in comparison to patients with IDCs (4.68 versus 2.95%, respectively). The main cause for this disparity was the higher number of T3–T4 and multicentric tumors at diagnosis among the ILC patients.

No differences were seen in the total number of sentinel lymph nodes removed and number/dimension of metastatic deposits between the two groups; however, at ALND, the number of patients with metastatic lymph nodes was higher in the ILC cohort (21 out of 40, 52.5%) in comparison to IDCs (45 out of 122, 36.9%). Moreover, 27.50% of patients with ILC had 3 or more metastatic lymph nodes at ALND after a positive SLNB versus only 11.48% of patients with IDC ($p=0.04$) (Figs. 2, 3 and 4).

The logistic univariate regression analysis showed that main factors associated with the risk of further metastatic deposits at ALND after positive SLNB were a number of positive lymph nodes > 2 (OR = 4.89, $p=0.02$) and, at the limit of statistical significance, pT3–4 tumors (OR = 4.07, $p=0.05$) and a non-luminal molecular subtype (OR = 2.74, $p=0.02$). Instead, the lobular histotype was not associated with the risk of further metastasis at ALND (OR = 1.62, $p=0.20$).

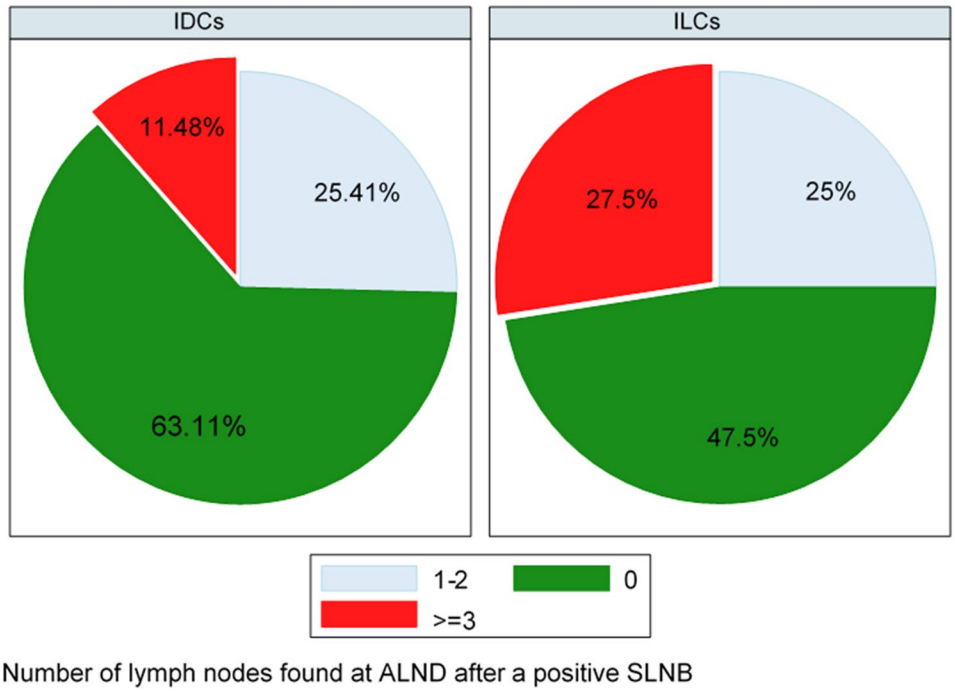

Fig. 2 Number of lymph nodes detected at ALND (Axillary Lymph Node Dissection) after positive SLNB (Sentinel Lymph Node Biopsy)

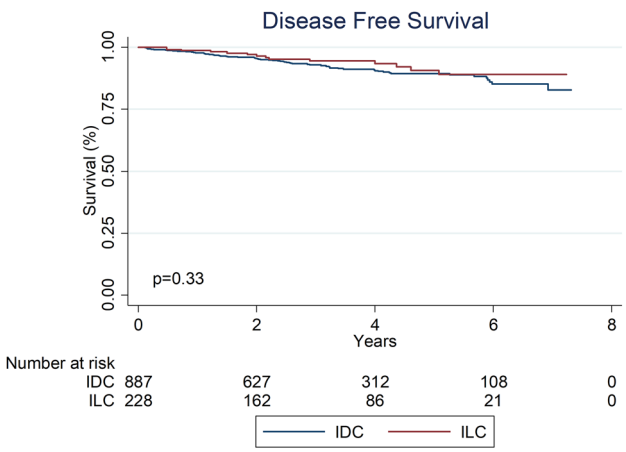

Fig. 3 Estimated Disease-Free Survival (DFS) according to tumor histotype. *IDC* invasive ductal carcinoma; *ILC* invasive lobular carcinoma

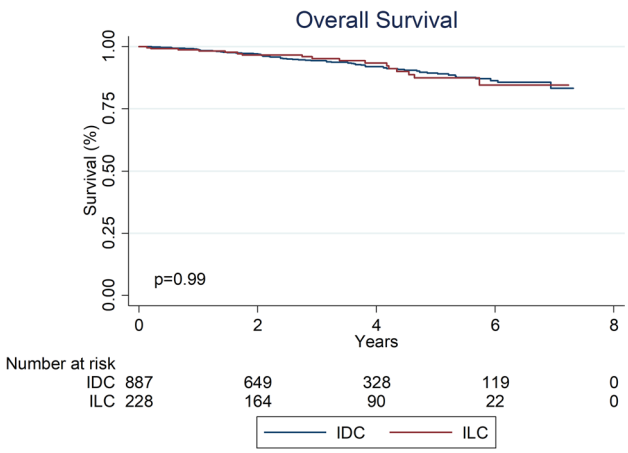

Fig. 4 Estimated Overall Survival (OS) according to tumor histotype. *IDC* invasive ductal carcinoma; *ILC* invasive lobular carcinoma

At the multivariate analysis, pT3–4 tumor (OR = 4.93, $p = 0.03$), the presence of > 2 positive lymph nodes at SLNB (OR = 4.72, $p = 0.03$) and non-luminal BC subtype (OR = 2.72, $p = 0.02$) were confirmed as strong predictors of further deposits (Table 3).

With a median follow-up of 3.18 years (0.13–7.32), predicted disease-free survival (DFS) at 5 years was 91% (95% CI 0.85–0.95) for ILC patients versus 89% (95% CI 0.86–0.92) for IDC patients ($p = 0.33$). Overall survival (OS) was 89% (95% CI 0.83–0.93) for ILC patients ($p = 0.99$) and 90% (95% CI 0.87–0.92) for IDC patients ($p = 0.99$).

At the multivariate analysis, the tumor histotype did not affect DFS or OS. The main parameters associated with the risk of recurrence were tumor's dimension (pT2, HR = 2.46, $p = 0.001$), nodal status (pN2–3, HR = 2.67, $p < 0.001$) and non-luminal molecular subtypes (Non-Luminal disease: HR = 1.85, $p = 0.01$) (Table 4). Variables impacting on the risk of death from any causes were age ≥ 60 years (HR = 4.25, $p < 0.001$), tumor size (pT2, HR = 2.46, $p = 0.002$ and pT3–4-, HR = 4.53, $p < 0,001$) and Ki67 ≥ 20% (HR = 1.86 $p = 0.008$). Nodal status impact on OS was at the limit of statistical significance (pN2–3, HR = 1.82, $p = 0.05$) (Table 5).

Table 3 Results of logistic regression analysis—univariable and multivariable—to identity predictive factors of further lymph node metastasis after positive SLNB

Variable	Univariable analysis Odds ratio (CI 95%)	*p* Value	Multivariable analysis Odds ratio (CI 95%)	*p* Value
Age				
< 60	Reference			
≥ 60	0.87 (0.46–1.64)	0.66		
Surgical procedure				
Conservative	Reference			
Mastectomy	1.26 (0.65–2.45)	0.50		
Grading				
I	Reference			
II	0.63 (0.11–3.55)	0.58		
III	1.12 (0.18–6.76)	0.90		
T Stage				
T1	Reference		Reference	
T2	1.76 (0.91–3.14)	0.09	1.60 (0.80–3.23)	0.19
T3–T4	4.07 (0.95–17.6)	0.05	4.93 (1.10–22.2)	0.03
Ki67				
< 20	Reference			
> = 20	0.77 (0.39–1.49)	0.44		
Number of Positive SLNB				
1	Reference		Reference	
2	1.83 (0.81–4.11)	0.14	1.85 (0.79–4.31)	0.16
> 2	4.89 (1.23–19.4)	0.02	4.72 (1.15–19.5)	0.03
Histotype				
IDC	Reference			
ILC	1.62 (0.77–3.41)	0.20		
Molecular Profile				
Luminal	Reference		Reference	
Non-Luminal	2.26 (0.99–5.27)	0.05	2.74 (1.16–6.50)	0.02

Multivariable model was performed including parameters assessed in the univariable analysis with a p value of less than the prespecified cut-off of 0.10. *IDC* invasive ductal carcinoma; *ILC* invasive lobular carcinoma

The subgroup analysis after patient stratification on the basis of Ki67 measurements showed that IDC tumors with Ki67 higher than 20% are characterized by the worst prognosis, both in terms of risk of recurrence and risk of death (Supplementary data, Figs. 1 and 2), whereas IDCs with lower Ki67 showed the best outcomes. Ki67 expression did not impact on prognosis in patients with ILC.

Discussion

The role of lymph node surgery was questioned after the results of the NSABP-04 trial [5] and later with the introduction of SLNB [6–8], which largely replaced ALND as a staging procedure. Furthermore, results from the ACOSOG Z0011 study underlined the absence of any survival benefit with the use of ALND in a population of clinically node-negative, SLNB-positive (≤ 2 lymph nodes), BC patients treated with BCS, adjuvant radiotherapy and, in most cases, adjuvant systemic therapy [4, 9].

While the best argument pro lymph node surgery is still the impact of axillary nodal status on prognosis, which guides adjuvant therapy decisions, this view has been questioned since publication of the results from two studies in 2009 and 2011, respectively [10, 11]. Moreover, with the increasing knowledge of breast cancer molecular subtype biological differences, it has become clear that each tumor subtype responds differently to adjuvant treatment, irrespective of nodal involvement.

As biology drives the choice of adjuvant systemic/targeted therapies, understanding BC subtype differences is paramount to tailor successful management strategies. The Oncotype DX molecular assay was used to analyze the risk of recurrence in 610,350 hormone positive tumor specimens [12]. Nodal status did not impact on the RS score in this study. On the other hand, RS distribution was correlated with tumor histology: a very small percentage of tubular,

Table 4 Results of Cox regression analysis—univariable and multivariable—for disease-free survival

Characteristics	Univariable analysis HR (95% CI)	*p* Value	Multivariable analysis HR (95% CI)	*p* Value
Age (Years)				
< 60	1.00 (Reference)			
≥ 60	0.97 (0.63–1.51)	0.90		
Surgical procedure				
Conservative	1.00 (Reference)		1.00 (Reference)	
Mastectomy	2.53 (1.64–3.89)	< 0.001	1.37 (0.84–2.24)	0.20
Tumor Size				
T1	1.00 (Reference)		1.00 (Reference)	
T2	3.92 (2.47–6.22)	< 0.001	2.46 (1.44- 4.22)	0.001
T3–T4	4.48 (2.42–8.95)	< 0.001	2.01 (0.88–4.59)	0.09
Lymph node metastasis				
N0	1.00 (Reference)		1.00 (Reference)	
N1	1.96 (1.16–3.19)	< 0.001	1.32 (0.75–2.33)	0.34
N2–N3	5.36 (3.25–8.23)	< 0.001	2.67 (1.49.4.78)	< 0.001
Ki67				
< 20%	1.00 (Reference)		1.00 (Reference)	
≥ 20%	2.37 (1.50–3.74)	< 0.001	1.53 (0.92–2.55)	0.10
Molecular profile				
Luminal	1.00 (Reference)		1.00 (Reference)	
Non-Luminal	2.53 (1.64–3.89)	< 0.001	1.85(1.13–3.01)	0.01
Histotype				
IDC	1.00 (Reference)			
ILC	0.75 (0.43–1.34)	0.33		

Multivariable model was performed including parameters assessed in the univariable analysis with a *p* value of less than the prespecified cut-off of 0.10. *IDC* invasive ductal carcinoma; *ILC* invasive lobular carcinoma

mucinous, cribriform, papillary and lobular histotypes showed RS ≥ 31, irrespective of nodal involvement.

Thus, the involvement of lymph nodes may not be the most important prognostic factor in ILC.

On the contrary, a SEER study on the impact of nodal metastasis on RS distribution showed that 5-year Breast Cancer Specific Mortality (BCSM) rate for RS ≥ 31 in node-positive patients was 14.3% versus only 0.4% in the node-negative population with RS < 18, emphasizing the contribution of nodal status in terms of prognosis [13].

Unfortunately, the vast majority of data on the impact of nodal status on BC outcomes was obtained from IDC patients. Only 7% of the patients enrolled on the Z0011 study had ILC and only 27 patients with ILC were randomized to receive SLNB plus ALND [4].

While a similar percentage of patients in both groups underwent SLNB (85%) in our study, the percentage of patients with metastasis at SLNB was higher in the ILC group (32.32% ILCs versus 24.19 IDCs, $p = 0.023$). This discrepancy could be explained at least in part by the fact that ILCs were on average bigger ($p < 0.001$) than IDCs and of a more advanced stage ($p < 0.001$) at diagnosis. In fact, it is well known that tumor dimension is one of the most important predictors of nodal involvement and SLNB positivity in BC [14–18].

A more advanced disease at diagnosis could also explain the greater lymph node involvement found at ALND in this cohort. The percentage of lymph node metastases at ALND was higher in ILC patients in comparison to IDCs, albeit this difference did not reach statistical significance. Importantly, the percentage of patients with ILCs who had 3 or more metastatic lymph nodes at ALND, after a positive SLNB, was 27.50% versus only 11.48% of patients with IDCs ($p = 0.04$). These results seem to confirm the most recent literature showing a higher rate of residual nodal disease after positive SLNB in patients with ILC in comparison to IDC [19–24]. Adachi et al. recently reported a very similar difference in the percentage of non-sentinel node metastases between ILCs and IDCs, with 68% of ILC patients having further metastatic deposits at ALND versus 46% of IDC patients [25].

However, our logistic regression analysis shows the absence of correlation between the lobular histotype and the risk of further metastases at ALND.

Fernández et al. looked at the N status of patients with grade-matched ILC and IDC and found a greater nodal involvement in patients with ILC, namely higher nodal stage

Table 5 Results of Cox regression analysis—univariable and multivariable—for overall survival

Characteristics	Univariable analysis HR (95% CI)	*p* Value	Multivariable analysis HR (95% CI)	*p* Value
Age (Years)				
< 60	1.00 (Reference)		1.00 (Reference)	
≥ 60	3.68 (1.95–6.95)	< 0.001	4.25 (2.22–8.14)	< 0.001
Surgical procedure				
Conservative	1.00 (Reference)		1.00 (Reference)	
Mastectomy	1.64 (1.07–2.52)	0.02	0.97 (0.56–1.66)	0.90
Tumor size				
T1	1.00 (Reference)		1.00 (Reference)	
T2	2.80 (1.73–4.54)	< 0.001	2.46 (1.40–4.13)	0.002
T3–T4	6.50 (3.59–11.76)	< 0.001	4.53 (2.02–10.19)	< 0.001
Lymph node metastasis				
N0	1.00 (Reference)		1.00 (Reference)	
N1	1.22 (0.70–2.11)	0.48	0.76 (0.42–1.38)	0.37
N2–N3	3.28(1.96–5.46)	< 0.001	1.82 (0.98–3.40)	0.05
Ki67				
< 20%	1.00 (Reference)		1.00 (Reference)	
≥ 20%	1.98 (1.26–3.11)	0.003	1.86 (1.18–2.94)	0.008
Molecular profile				
Luminal	1.00 (Reference)			
Non-Luminal	1.89 (0.86–2.25)	0.18		
Histotype				
IDC	1.00 (Reference)			
ILC	1.00 (0.59–1.71)	0.98		

Multivariable model was performed including parameters assessed in the univariable analysis with a *p* value of less than the prespecified cut-off of 0.10. *IDC* invasive ductal carcinoma; *ILC* invasive lobular carcinoma

at the time of surgery, a greater number of total positive nodes, and a higher ratio of positive nodes [19]. Van Wyhe et al. reported similar results in stage-matched patients: ILC patients were more likely to have a greater total number of positive axillary nodes at the time of surgery and a larger tumor size in comparison to patients with IDC [26].

Opposite results were reported in another study comparing clinical and biological features of a large number of patients with ILC or IDC [27]. The authors showed that, while tumor size was significantly bigger for ILCs at the time of diagnosis, nodal involvement rate was similar in both cohorts.

Additionally, intrinsic molecular features could contribute to the later stage diagnosis and therefore the greater nodal involvement observed in lobular cancers. Li et al. found that both, ILC and mixed ductal/lobular carcinomas, were more likely to be diagnosed at an advanced stage (stage III/IV), to have large tumor size (> 5 cm), and to be node positive when compared with IDCs [28].

The number of completion lymphadenectomies requiring a second operation after a negative intra-operative SLND was higher in the ILC group in comparison to IDC patients. A higher rate of false negatives at intra-operative evaluation of sentinel nodes in ILCs could explain this result. It has been previously reported that this procedure may present more challenges in the lobular subtype [29–31]. Reasons for this may include the typical "single-cell" pattern of infiltration of lobular cancer, and a much lower pathologist's exposure to this molecular subtype, due to ILCs modest numbers.

Of note, molecular techniques for intra-operative evaluation of sentinel nodes, such as the One-Step Nucleic Acid Amplification (OSNA), are available and could represent a reasonable approach to decrease the false-negative rate of SLN metastases from ILCs. Unfortunately, standardization of OSNA results, translation into the TNM classification and validity of the technique as a decision tool for further axillary therapy are still subject of debate and histology confirmation of disease is still needed [32].

The larger number of further metastases found at ALND after positive SLNB in lobular cancer patients does not appear to translate into survival outcomes differences, even though our study is underpowered to detect them, due to a short follow-up period and the much smaller number of ILCs in comparison to IDCs. However, this tendency is in accordance with findings by other studies [12, 33, 34]. In fact, even with the limitations stated above, we found no difference in predicted 5-year DFS and OS between the lobular and ductal

histotypes. The N stage, as the T, influences prognosis when greater than 2, irrespective of tumor histotype.

A non-luminal biological subtype of cancer was associated with higher risk of recurrence, indirectly confirming that biology, more than purely nodal involvement, may drive the risk of local and distant recurrence. These data are also supported by our Ki67 subgroup analysis, showing that IDCs with Ki67 higher than 20% (i.e., luminal B cancers) [35] have worse prognosis when compared to IDCs with low Ki67 or with ILCs (Supplementary Figs. 1 and 2).

The underlying assumption of the Z0011 trial was the possibility to treat patients with SLN metastases with selected systemic therapies according to the biological characteristics of each cancer. Unfortunately, classic ILCs show lower degree of response to chemotherapy in comparison to IDC and a generally low chemo-sensitivity [9, 36]. Given the most common biological profile, adjuvant endocrine therapy, rather than other systemic therapies, is most likely to be effective in ILC, as previously shown in a large Early Breast Cancer Trialists Collaborative Group meta-analysis [37]. In particular, although ILC-specific studies are limited, some data obtained from an ad hoc analysis of the BIG 1–98 trial suggest a greater benefit of letrozole compared to tamoxifen [38]. The only exclusion to this could be pleiomorphic ILC, which over-expresses HER2 in up to 80% of cases and is therefore amenable to targeted anti-HER2 therapy and, in some cases, chemotherapy [39].

Finally, there is a lack of studies looking at ILCs outcomes after adjuvant radiotherapy (RT). The available data showed no difference in clinical outcomes between IDCs and ILCs. If we consider breast-conserving management as the sum of BCS plus RT, patients with ILC show the same rates of loco-regional recurrence than IDC patients, in the presence of negative margins at surgery [40, 41]. Also, Stecklein and colleagues looked at post-mastectomy RT and found the same benefit from RT in ILCs and in IDCs [42]. Given the relatively low representation of ILC, though, further studies may be needed to evaluate this aspect.

This work has limitations: mainly, the low number of ILCs in comparison to IDCs, which is a common issue related to the prevalence of the lobular histotype, and the retrospective nature of the study. Also, due to the short follow-up period and the limited number of ILCs, the study is underpowered to detect differences in survival outcomes. Finally, our nodal involvement analysis results are pooled together and not stratified according to the disease stage.

Conclusions

Our analysis confirmed a higher rate of further nodal involvement after positive SLNB in ILC in comparison to IDC. However, the prognostic significance of this difference remains unclear and further prospective studies are needed.

While at present loco-regional and systemic treatment approaches are the same among all breast cancer types, advances in the understanding of the molecular basis of the lobular type will hopefully allow development of much needed, specifically tailored, treatment algorithms.

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Compliance with ethical standards

Conflict of interest The authors Silvia Paola Corona, Marina Bortul, Serena Scomersi, Chiara Bigal, Fabrizio Zanconati, Stephen Fox, Fabiola Giudici, and Daniele Generali declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was not applicable for this study.

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