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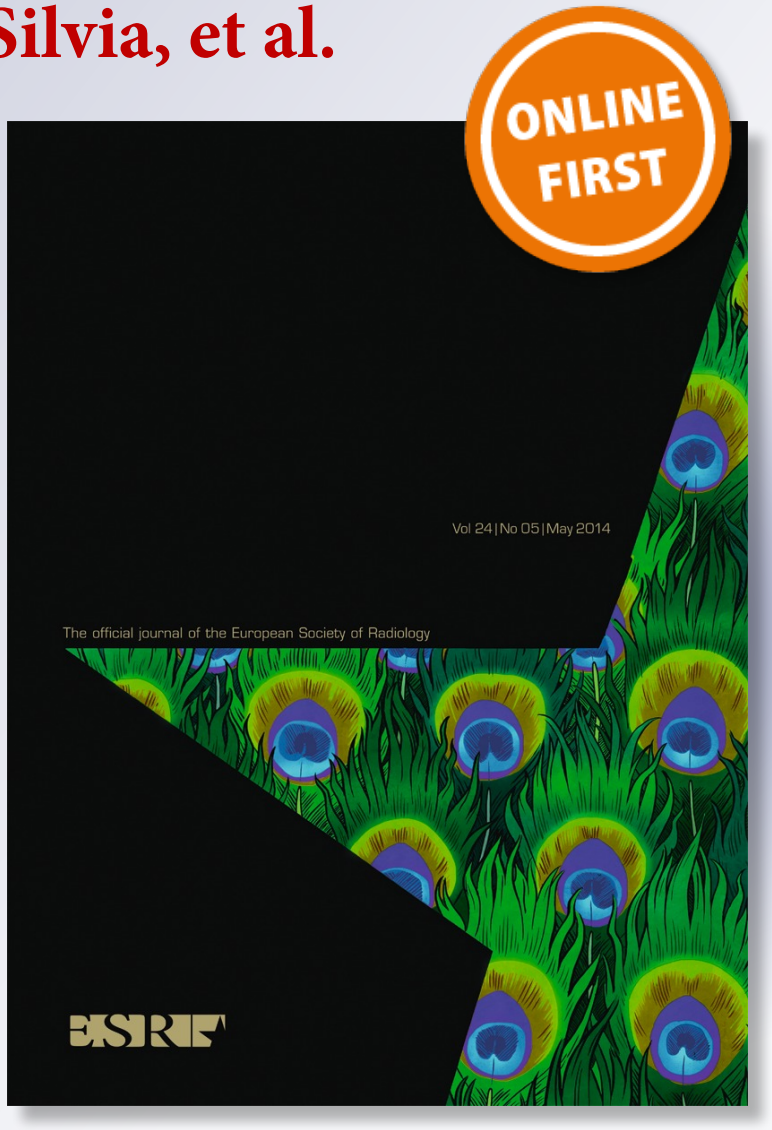

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Abstract
Objectives To evaluate the underestimation rate and clinical relevance of lobular neoplasia in vacuum-assisted breast biopsy (VABB).
Methods A total of 161 cases of LN were retrieved from 6,435 VABB. The histological diagnosis was ALH (atypical lobular hyperplasia) in 80 patients, LCIS (lobular carcinoma in situ) in 69 patients and PLCIS (pleomorphic lobular carcinoma in situ) in 12 patients. Seventy-six patients were operated on within 2 years after VABB and 85 were clinically and radiologically monitored. The mean follow-up was 5.2 years, and the prevalence of malignancy was evaluated in the group of 85 patients.
Results The clinico-pathological characteristics significantly favouring surgery were larger lesions, occurrence of a residual lesion following VABB and histological LCIS and PLCIS subtypes. The VABB underestimation rate as compared to surgery was 7.1 % for ALH, 12 % for LCIS and 50 % for PLCIS. Overall, 11 of the 148 patients included in this survival analysis developed an ipsilateral tumour.
Conclusion Although obtained retrospectively in a relatively small series of patients, our data suggest that only patients with a diagnosis of PLCIS in VABB should be treated with surgery, whereas patients with ALH and LCIS could be monitored by clinical and radiological examinations.
Key Points
- *The treatment of ALH and LCIS in VABB is still debated*
- *Some authors favour radical treatment and others a more conservative approach*
- *Only patients with PLCIS in VABB should be treated by surgery*

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Keywords Breast cancer · Lobular neoplasia · Vacuum-assisted breast biopsy · Non-palpable breast lesions · Breast carcinoma in situ

Abbreviations

ADH	Atypical ductal hyperplasia
ALH	Atypical lobular hyperplasia
BI-RADS	Breast imaging reporting and data system
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
IDC	Invasive ductal cancer
ILC	Invasive lobular cancer
LCIS	Lobular carcinoma in situ
LN	Lobular neoplasia
MRI	Magnetic resonance imaging
PLCIS	Pleomorphic lobular carcinoma in situ
TDLU	Terminal duct lobular unit
US	Ultrasound
VABB	Vacuum-assisted breast biopsy

Introduction

Lobular in situ proliferations represent a breast disease histologically characterized by the proliferation of small discohesive epithelial cells in the terminal duct lobular unit (TDLU), which may be associated with pagetoid spread to the terminal ducts [1]. They are classified into two main entities, atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) [2], based on the histological pattern of involvement of the TDLU. More recently, the occurrence of a lobular in situ disease characterized by the proliferation of highly pleomorphic cells associated with central necrosis has been repeatedly reported and termed pleomorphic lobular carcinoma in situ (PCIS) [3–9]. ALH and LCIS are usually incidentally detected in core biopsies from patients with a variety of breast tissue abnormalities detected by clinical examination, ultrasound or mammography. Although their prognostic relevance remains to be established, a few studies dealing with a small population of patients with long-term follow-up reported a low incidence of invasive carcinoma [2, 3, 9–14].

The prevalence of LN in otherwise benign core biopsies ranges from 0.5 % to 4 % [3, 11, 13, 15–17], and has increased in recent years owing to the widespread use of digital mammography, VABB, larger biopsy needles and more sensitive laboratory techniques, such as immunohistochemistry [3]. The therapeutic approach to ALH and LCIS is controversial [18]: some authors favour surgery or radiotherapy, considering them [3, 4, 17, 19–21] as precursors of invasive cancer, whereas others suggest that ALH and LCIS are a high-risk condition which should therefore be closely monitored by clinical and radiological (US, mammography, MRI) means [11, 13, 14, 16, 22–27], or treated in specific pharmacoprevention trials, such as those administering low-dose tamoxifen [28]. On the other hand, PLCIS is classified as a B5 lesion, thus generally requiring open surgery, and it has been reported to be associated with a high risk of developing subsequent invasive cancer [3–8, 29].

In order to shed light on the underestimation rate of ALH, LCIS and PLCIS diagnosed in VABB compared to surgery and its clinical relevance, we investigated a consecutive series of 236 cases retrieved from 6,435 procedures performed in a single institution over a 9-year period.

Methods

Patients

Clinico-pathological data of 6,435 patients subjected to VABB procedures in our institution between 2001 and 2009 were retrieved from our electronic database. Stereotactic and US-guided biopsies were performed using 11-gauge vacuum-assisted needles with a 19.1-mm-long trough or with 8-gauge vacuum-assisted needles with a 23-mm-long trough.

Only patients with ALH, LCIS and PLCIS in the absence of further lesions classified as B3, B4 or B5 [29] were included in the study.

When ALH, LCIS and PLCIS occurred in the same specimen, the highest histological grade was registered for statistical purposes. Seventy-three (30.9 %) of these patients were excluded from the study owing to a past or present history of previous or concurrent histologically proven ipsilateral or contralateral carcinoma, comprising invasive ductal carcinoma, invasive lobular carcinoma, ADH, any DCIS or PLCIS. Patients with previous PLCIS were excluded from the study because this condition has been reported to be biologically different from ALH and LCIS [3–8, 29], and frequently associated with local relapse and invasive cancer. Two further patients were withdrawn because they were lost at follow-up.

The following clinico-pathological parameters were evaluated: age of the patient, site of the lesion, imaging characteristics, Breast Imaging Reporting and Data System (BI-RADS) score and size of the lesion on conventional imaging (mammography and US), presence of residual disease on post-VABB imaging, number of bioptic specimens and duration of follow-up (2–11 years).

The underestimation rate of LN was defined as the occurrence of DCIS or any invasive carcinoma in the ipsilateral breast samples surgically excised within 2 years after the VABB [29]. The diagnosis obtained in VABB specimens was used as the standard reference when compared to post-surgery histology.

The occurrence of DCIS, PLCIS and/or any invasive carcinoma diagnosed in ipsilateral surgical samples 2 years after completing the VABB procedure was considered as malignancy during follow-up, because, in keeping with the European guidelines [29], it is not necessarily correlated with LN. Patients with an uneventful clinical and radiological follow-up lasting at least 2 years, and who were never operated on thereafter, have been defined as without diagnostic underestimation.

Statistics

The Mantel–Haenszel test for trend and the Fisher's exact test were used to evaluate the association between respectively ordinal (e.g. dimensions) and categorical (location) variables and VABB underestimation.

The relevance of LN diagnosed by VABB for the prediction of ipsilateral breast tumour relapse was evaluated only in patients without previous surgery, if the open biopsy result was either an ALH or LCIS lesion, or any benign disease. As a matter of fact, all the patients included in the study with a diagnosis of DCIS and invasive cancer after surgery received at least an adjuvant therapy (hormonal therapy, chemotherapy or radiotherapy), potentially affecting the analysis. The event rate was calculated by dividing the number of events by the number of patient-years at risk. Disease-free survival (DFS) was calculated from the date of VABB to the date of the last follow-up or to the date of diagnosis of ipsilateral malignant disease. DFS plots were elaborated using the Kaplan–Meier method. Patients were stratified by age, location of the lesions, microcalcifications distribution pattern (single cluster, multiple clusters or diffuse), mammographic features (microcalcifications, opacity, distortion, opacity with microcalcifications) and BI-RADS score. The following criteria were also assessed: imaging lesion size, LN subtype (ALH, LCIS and PLCIS), number of obtained specimens, and occurrence of microcalcifications as evaluated by x-ray, presence of residual disease on post-VABB imaging (complete or incomplete excision by VABB), type of biopsy (stereotactic or ultrasound guided), and needle core thickness (8/11G). The log-rank and Wilcoxon tests were used to evaluate the difference between DFS and the considered variables. All the analyses were performed using the SAS software (version 8.2, Cary, NC).

Results

Of the 161 patients representing the study population, 80 had ALH (49.7 %), 69 LCIS (42.9 %) and 12 PLCIS (7.4 %) in VABB. The main clinico-pathological characteristics of the study population are detailed in Table 1: the mean age was 51 years (range 32–77), and the mean follow-up was 5.2 years (range 2–11).

Seventy-six patients were operated on within 2 years after VABB, and the final diagnosis in the surgical specimens was ALH (nine cases), LCIS (41 cases), PLCIS (two cases), ILC (seven cases), ADH (one case), DCIS G1 (two cases), DCIS G2 or G3 (one case each), IDC (two cases) or benign disease (10 cases). In particular, the 14 patients with ALH in VABB had benign lesions, ALH, LCIS (4 cases each), ADH or ILC (one case each) at surgery; the 50 patients with LCIS had benign lesions (six cases), ALH (five cases), LCIS (33 cases), DCIS G1 (two cases), DCIS G2 (one case), IDC (two cases) or ILC (one case) at surgery; and the 12 patients with PLCIS had LCIS (4 cases), PLCIS (two cases), DCIS G3 (one case) or ILC (5 cases) at surgery. The two cases of PLCIS at surgery were considered as clinically benign lesions because the resection margins were histologically free of disease: one patient developed an IDC in the same quadrant 7.6 years later, whereas the remaining patient was never operated on and is free of disease 4.3 years after surgery. Overall, eight of the 76 patients operated on within 2 years after VABB were subjected to a re-operation in the same quadrant after a mean period of 5.3 years (range 2.6–9.3), and received a diagnosis of PLCIS (one case), ILC (two cases) and IDC (five cases). In particular, the five patients with LCIS at first surgery (and in VABB) had PLCIS (one case) and ILC or IDC (two cases each); the two cases of DCIS G1 at first surgery (with LCIS in VABB) had IDC; as mentioned above, the single case of PLCIS at first surgery (and VABB) had a diagnosis of IDC.

The clinico-pathological characteristics significantly favouring surgery within 2 years after VABB were larger lesions ($p=0.01$), the occurrence of a residual lesion following VABB ($p=0.0008$) and LN subtype (LCIS and PLCIS) ($p<0.0001$) (Table 1). In particular, 40/47 (85.1 %) patients with lesions measuring 10 mm or more and with residual disease after VABB and LCIS/PLCIS underwent surgery. The remaining seven patients (15 %) had not developed any malignancy at the last follow-up. In contrast, only 2/23 (8.7 %) patients with nodules measuring less than 10 mm, without residual disease and ALH histology were operated on.

The underestimation rate was evaluated in the group of 76 patients (76/161, 47.2 %) who received surgery within 2 years after VABB (results of primary VABB: 14 ALH, 50 LCIS and 12 PLCIS). Thirteen (1 ALH, 6 LCIS and 6 PLCIS) of these 76 patients had a final diagnosis of malignancy in their surgical specimens (seven ILC, two IDC, two DCIS G1, one DCIS G2 and one DCIS G3). In particular, the patient with ALH in VABB had an ILC at surgery, the six patients with LCIS had ILC, DCIS G2 (one case each), IDC or DCIS G1 (two cases each), and the six patients with PLCIS at VABB had ILC (five cases) or DCIS G3 (one case). As a consequence, the overall VABB underestimation rate as compared to surgery was 17 % and in particular 7.1 % for ALH (1/14), 12.0 % for LCIS (6/50) and 50.0 % for PLCIS (6/12) ($p<0.0001$). Among the clinical and imaging characteristics analysed, only BI-RADS

Table 1 Association between characteristics at VABB and surgery

		Surgery within 2 years after VABB				*p* value
	All	No		Yes		
	n	*n*	%	*n*	%	
All	161	85	52.8	76	47.2	
VABB						
Stereotactic	144	74	51.4	70	48.6	
US guided	17	11	64.7	6	35.3	0.32
US and mammography features						
Distortion	3	2	66.7	1	33.3	
Opacity	19	11	57.9	8	42.1	
Microcalcification	130	65	50.0	65	50.0	
Distortion + microcalcification	5	5	100.0			
Opacity + microcalcification	4	2	50.0	2	50.0	0.23
Microcalcification features						
Clusters	84	47	56.0	37	44.0	
Multiple clusters	11	6	54.5	5	45.5	
Diffuse	43	18	41.9	25	58.1	0.32
Size (mm)						
<10	45	30	66.7	15	33.3	
10–20	67	37	55.2	30	44.8	
>20	49	18	36.7	31	63.3	Trend 0.01
Residual lesion at imaging after VABB						
No	76	51	67.1	25	32.9	
Yes	85	34	40.0	51	60.0	0.0008
LN subtype at VABB						
ALH	80	66	82.5	14	17.5	
LCIS	69	19	27.5	50	72.5	
PLCIS	12			12	100.0	<0.0001
Number of bioptic samples at VABB						
0–9	22	14	63.6	8	36.4	
10–14	61	39	63.9	22	36.1	
15–19	51	21	41.2	30	58.8	
20+	27	11	40.7	16	59.3	Trend 0.01
Number of bioptic samples with microcalcifications at VABB						
0–4	45	29	64.4	16	35.6	
5–9	79	36	45.6	43	54.4	
10–14	31	17	54.8	14	45.2	
15+	6	3	50.0	3	50.0	Trend 0.32
Number of bioptic samples without microcalcifications						
0–4	40	27	67.5	13	32.5	
5–9	77	34	44.2	43	55.8	
10–14	26	15	57.7	11	42.3	
15+	18	9	50.0	9	50.0	Trend 0.33
Needle size						
8 G	8	3	37.5	5	62.5	
11 G	153	82	53.6	71	46.4	0.48

LN lobular neoplasia, *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma in situ, *PLCIS* pleomorphic lobular carcinoma in situ, *VABB* vacuum-assisted breast biopsy, US ultrasound

score (p=0.02) was significantly associated with diagnostic underestimation.

The incidence of malignancy during follow-up was evaluated in the group of 85 patients which had not been operated on within 2 years, including 72 patients who were never subjected to surgery, and 13 patients operated on after 2 years for ipsilateral (five patients, 5.9 %; one ILC, three IDC and one DCIS G1) or contralateral (eight patients, 9.4 %; seven IDC and one DCIS G1) disease (Fig. 1). In all 13 patients operated on 2 years or more after VABB, the malignancy developed in the same quadrant as the preceding primary VABB. These 85 patients were considered a specific and homogeneous subgroup because, in accordance with European guidelines [27], a malignancy developing 2 years after a previous diagnosis in VABB does not necessarily represent a relapse or an evolution from a pre-existing in situ disease, and may therefore be considered a de novo malignancy. According to these criteria, the incidence of malignancy during follow-up was 4.5 % for ALH (3/66; two IDC and one DCIS G1) and 10.5 % for LCIS (2/19; one ILC and one IDC), whereas all patients with PLCIS in VABB underwent surgery within 1 year.

We also ascertained the prognostic relevance of clinical, imaging and pathological characteristics (LN type at VABB, age, location of the lesions, microcalcifications distribution pattern, mammographic features, BI-RADS score, number of obtained specimens and occurrence of microcalcifications as evaluated by x-ray, imaging lesion size, presence of residual disease after VABB as evaluated by imaging, method of biopsy and needle core thickness). For this purpose, we excluded from the analysis the 13 patients receiving a diagnosis of any invasive carcinoma or DCIS in surgical specimens within 2 years after VABB, because it was not possible to rule out that the malignancy originally coexisted with LN, and was therefore underestimated by the VABB procedure [27]. The eight events developing in the contralateral breast were also not included in the survival analysis, because they were uninformative about the clinical value of the characteristics listed above (Fig. 1).

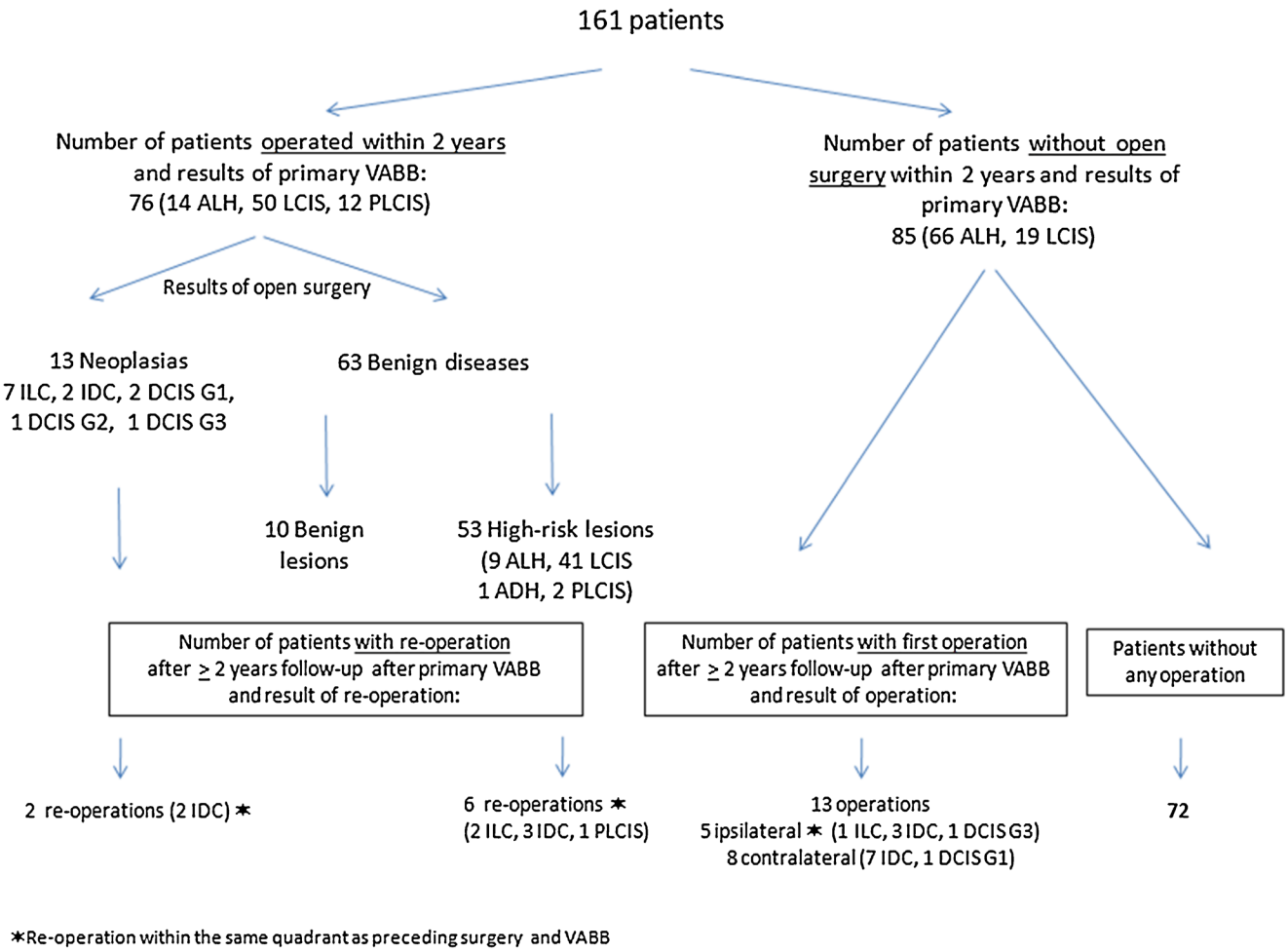

Fig. 1 Flow chart of patients' treatment and follow-up after VABB: *pts* patients, *LN* lobular neoplasia, *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma in situ, *PLCIS* pleomorphic lobular carcinoma in situ, *DCIS* ductal carcinoma in situ, *ILC* invasive lobular cancer, *IDC* invasive ductal cancer, *VABB* vacuum-assisted breast biopsy

Overall, of the 148 patients included in this survival analysis, 11 (7.4 %; three ALH, seven LCIS, and one PLCIS at VABB) developed an ipsilateral tumour (six IDCs, three ILCs, one DCIS G1 and one PLCIS), located in the same quadrant as the VABB, after a mean follow-up of 5.2 years. In particular, the prevalence of ipsilateral tumours was 3/79 (3.8 %) in patients with ALH in VABB, 7/63 (11.1 %) in LCIS and 1/6 (16.7 %) in PLCIS. Interestingly, six (54.5 %) of these patients were operated on twice, and the first intervention, carried out within 2 years after VABB, yielded a histological diagnosis of benign disease.

Among the clinico-pathological features analysed, the only characteristic significantly associated with a reduced DFS was the occurrence of multiple clusters or a diffuse microcalcifications pattern (p=0.04) (Fig. 2).

Discussion

In the present study, we evaluated the underestimation rate and clinical relevance of LN diagnosed in VABB. Owing to its complexity in histological, clinical, biological and imaging characteristics [15], the spectrum of intralobular proliferations is classified into three main histological subtypes (ALH, LCIS and PLCIS) [30].

The reported prevalence of LN in breast biopsies is low, accounting for less than 4 % [3, 11, 13, 15–17]. In line with this figure, we found LN in 3.6 % of our breast biopsies. Although the actual incidence and prevalence of LN in the general population are unknown because it is usually not associated with clinical signs and symptoms, it has been reported that ALH and LCIS are more frequent in younger women (mean age 50 years), as compared to PLCIS (55 years). Nevertheless, in the population included in this study, there was no significant correlation between age and the histological type of LN.

The management of patients with a diagnosis of ALH and LCIS is still controversial, but basically rests on two main therapeutic approaches, conservatory treatment or surgery. The rationale of the conservative approach (close follow-up [11, 13–17, 26, 27] or chemoprevention [28]) relies on the hypothesis that LN may be a risk factor for developing breast cancer (8- to 10-fold higher risk as compared to the general population) [31, 32], whereas the adepts of surgical treatment argue that LN is a non-obligate precursor of invasive breast cancer, therefore requiring an aggressive local treatment (surgery/radiotherapy) [3, 4, 15, 17, 19–21]. On the other hand, there is general consensus to treat all patients with PLCIS diagnosed by bioptic procedures with open surgery. Similarly to DCIS, the diagnosis of LN in VABB (with or without further surgical radicalization) may underestimate a concurrent malignancy. As a matter of fact, the probability of unveiling a breast malignancy at the site of a previous biopsy yielding a diagnosis of LN varies from 15 % to 33 % in the reported experiences [27, 33–35], although it may drop to 4 % if the lesion is completely excised during the bioptic procedure [36]. These discrepancies may be due to selection criteria, such as the inclusion of patients with a previous history of breast carcinoma [13, 21, 25–27], or the coexistence of high-risk lesions. In addition, the data are usually extrapolated from heterogeneous, multicentric series of patients assessed using different diagnostic criteria on either core or vacuum-assisted biopsies [20, 21, 25, 27, 37]. In this regard, it is worth noting that the diagnosis of LN in biopsies obtained using VABB with larger needles is

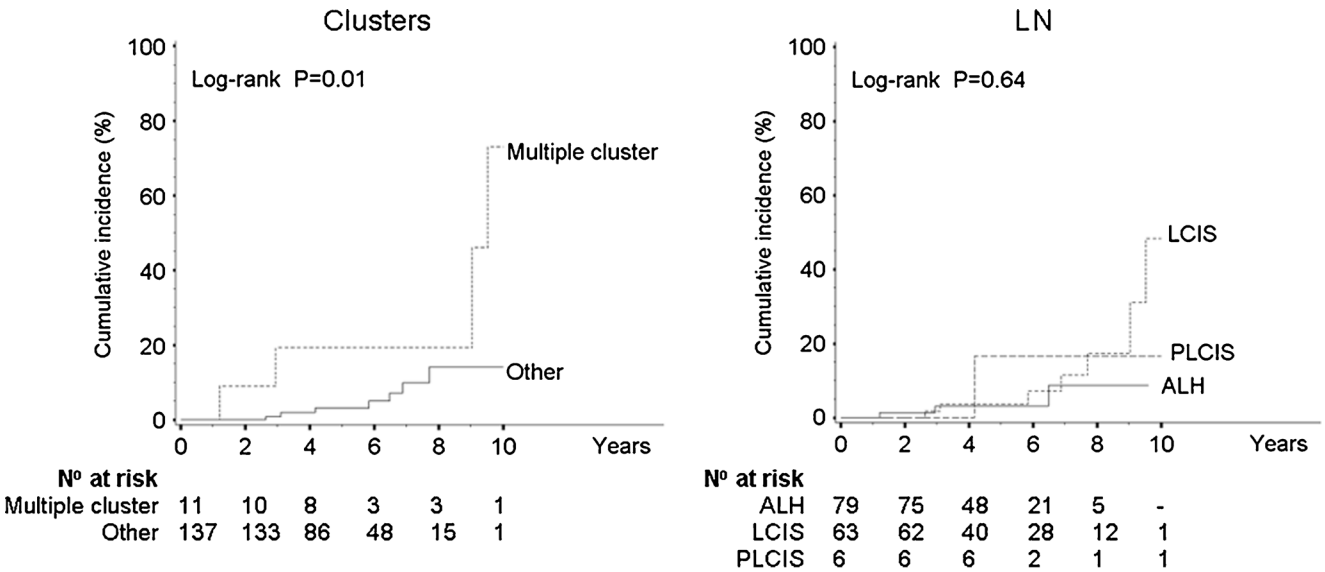

Fig. 2 Rate of ipsilateral breast events in 148 patients according to the presence of multiple calcified clusters at VABB and LN. *LN* lobular neoplasia, *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma in situ, *PLCIS* pleomorphic lobular carcinoma in situ

associated with a disease underestimation risk lower than that of the traditional core biopsy.

In line with these data, the overall underestimation rate in our series was 17 %, and the prevalence of malignancy during follow-up in the group of ALH and LCIS patients who were not operated on or were subjected to surgery 2 years or more after VABB was 15 %. It is worth noting that we restricted our analysis to patients without a history of previous and concurrent breast malignancy or high-risk disease and did not include patients with a diagnosis of LN obtained in core biopsies.

Interestingly, we reported that the underestimation rate was associated with the LN histological subtype, being significantly ($p<0.0001$) higher in cases of PLCIS as compared to ALH and LCIS. The underestimation rate according to the histological subtype was very wide, ranging from 50 % for PLCIS to 7 % for ALH. Accordingly, the underestimation rate reported by Hwang et al. [36] in a population of 333 patients was 2 % for ALH, 11 % for classic LCIS and 46 % for the pleomorphic variant. Taken together, these data are in line with recent studies identifying PLCIS as a particularly aggressive entity [3–8] that therefore deserves to be classified [29] as B5 (similarly to DCIS) in bioptic specimens, thus distinguishing it from ALH and LCIS, currently classified as B3. Our findings may therefore justify the higher underestimation rate reported in previous studies, dealing with patient cohorts which have not been classified according to the histological LN subtype. Although retrospectively obtained in a relatively small series of patients, the data stemming from our analysis are robust enough to generate the hypothesis that only patients with a diagnosis of PLCIS in VABB should be treated by surgery, whereas patients with ALH and LCIS could be monitored by clinical and radiological means, possibly including MRI [22–24]. In this regard, it has to be underlined that the treatment of LCIS is still a matter of debate, although close clinical and radiological follow-up ("wait and see") is generally preferred to surgery. Along this line, only 43.0 % (64/149) of patients with ALH and LCIS in VABB were treated by surgery in our series, with a trend towards a decrease over time, and the prevalence of patients who developed an ipsilateral malignancy was similar among the groups treated by surgery (6/11, 54.5 %) and clinically monitored (5/11, 45.5 %).

The surgical management of patients with ALH and LCIS in VABB is also debatable. We found that the clinicopathological characteristics significantly favouring surgery in our series were larger lesions, the occurrence of a residual lesion following VABB and histological diagnosis of LCIS or, as expected, PLCIS. Nevertheless, there was not a single characteristic pointing toward surgery, and the decision to operate usually stemmed from an integrated evaluation of the clinical, radiological and pathological parameters.

Although based on a small number of events, our data suggest that a wide surgical excision of the breast tissue adjacent to the VABB site does not protect LN patients from the occurrence of more aggressive diseases. Likewise, the significant number of contralateral breast cancers observed in our study (5 %) fosters a more conservative approach including close follow-up and chemoprevention.

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