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Risk and Predictive Factors of Rate of Lymph Node Invasion in Breast Cancer with Axillary Involvement

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Abstract

Purpose: Breast cancer is the most common cancer among women in France. Axillary lymph node invasion has a major prognostic impact. The aim of this study was to evaluate the risk and predictive factors of the rate of lymph node invasion in breast cancer with axillary involvement.

Methods: A retrospective study was conducted at the Lorraine Cancer Institute between 1 January 2014 and 31 December 2015. It included patients with breast cancer who underwent breast surgery associated with ALND (either immediately in case of positive FNAC, or secondarily in case of positive SLNB).

Results: In total, 194 patients were included. 99 underwent SLNB and ALND after (Group 1), 95 had a positive node in the FNAC and underwent ALND (Group 2). Multivariate analysis shown that only age at diagnosis (RR 2.79 [1.27; 5.74]), ultrasound tumor size (RR 2.97 [1.20; 7.64]), LVSI (RR 1.88 [1.07; 2.74]), multifocality (RR 2.27[1.35; 5.41]) and high histological grade (RR 3.38 [1.45; 9.74]) were significantly associated with a high axillary involvement. There was a 1.28% recurrence rate at 5 years in Group 1, compared with 28.21% recurrence rate at 5 years in Group 2 ($p<0.001$).

Conclusion: Age, tumor size (on ultrasound), lymphovascular invasion, multifocality and histological grade are risk and predictors factors of the rate of lymph node invasion. Preoperative positive FNB have a greater degree of lymph node involvement and a worse overall and progression-free survival than patients whose lymph node involvement was discovered at the time of the SLNB.

Keywords: Breast cancer; Axillary involvement; Risk factors, Predictive factors; Axillary lymph node dissection.

Introduction

In France, breast cancer is the leading cancer in women with approximately 58,500 new cases each year. It is also the main cause of death by cancer in women, with 12,146 deaths per year [1,2].

Axillary lymph nodes are frequently the first area of invasion and have in patients a major prognostic impact. The 5-year survival for patients with breast cancer without axillary involvement is 98.8%, whereas survival for patients with axillary involvement is 85.8% [3].

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Lymph node status must be assessed at diagnosis, at the same time as the breast examination. The clinical examination should be associated with an imaging examination. In most cases, an axillary ultrasound is preferred. In case of suspicious adenopathy, a Fine Needle Aspiration Cytology (FNAC) or a lymph node biopsy should be performed [4].

Breast and axillary examination are classified using the TNM classification. The treatment is adapted according to this. At present, for TNM T1 and T2 breast tumors, in addition to the breast surgery, a Sentinel Lymph Node Biopsy (SLNB) is performed in the absence of suspicious adenopathy or in the case of negative axillary biopsy. In some cases, it is also possible to perform a SLNB for small T3 and T4b tumors, after discussion in a multidisciplinary meeting [5].

In case of lymph node invasion and several suspicious lymph nodes involvement, the surgical treatment consists of an Axillary Lymph Node Dissection (ALND), performed in addition to the breast procedure. This method presents more complications such as infections, lymphoceles, reduction of brachial mobility, chronic pain and lymphedema [6,7].

Since 2022 the French recommendations allow a SLNB only approach to be performed in the absence of suspicious adenopathy, or a single lymph node metastasis, if the ACOSOG Z0011 [8] criteria are met [5].

In addition, several studies have shown that performing a SLNB alone has a similar prognosis in terms of survival and disease control as performing an ALND alone or as an adjunct in T1 or T2 stage disease [8-10].

At the time of this therapeutic decrease, it is important to know if there are risk factors and predictive factors of lymph node invasion. This could allow, for cases with a high risk of axillary involvement, to propose an intraoperative examination at the time of the SLNB or an ALND from the outset in order to avoid a surgical recovery.

In this context, the aim of this study was to highlight the risk and predictive factors of the rate of lymph node involvement in breast cancer in patients with positive axillary FNAC and positive SLNB.

Material and methods

Data were retrieved retrospectively from the Hospital Database of the Department of Surgical Oncology at the Lorraine Cancer Institute, France, between 1 January 2014, and 31 December 2015.

Inclusion criteria

Women diagnosed with breast cancer, classified cT1 to cT3, cN0 or cN, and who underwent breast surgery associated with ALND (either immediately in case of positive FNAC, or secondarily in case of positive SLNB), between January 1, 2014 and December 31, 2015 were included. They are classified in two groups: Group 1 corresponds to patients who underwent SLNB and ALND after. Group 2 corresponds to patients who had a positive node in the FNAC and who underwent ALND at the outset.

Patients who received neoadjuvant chemotherapy and patients for whom preoperative workup data were unavailable were excluded. The exclusion criteria were T4 classified tumors, ductal carcinoma in situ, men, metastatic lesions, breast or axillary recurrence, and patients treated with neo-adjuvant chemotherapy or with unavailable preoperative workup.

Population characteristics

To determine predictive factors associated with node involvement, demographic and histological data were evaluated for each patient: age, weight, height, carcinological history, BRCA mutation, clinical stage T and N, tumor size, multifocality in the breast, type of surgery [Breast-Conserving Surgery (BCS) or total mastectomy, SLNB, ALND], final histological results [tumor size, histological type, Scarff-Bloom-Richardson (SBR) grade, Ki67 rate, estrogen and progesterone receptors, HER2 status], presence of Lymphovascular Space Invasions (LVSI), number of involved lymph nodes and the presence of extracapsular effraction. Immunohistochemical classification subtypes of breast cancers were defined as Luminal A (estrogen and progesterone receptors >10%, Ki67 ≤20% and negative HER2 immunohistochemical staining) Luminal B (estrogen receptor >10% and progesterone receptors <10% or Ki67>20%), basal-like (estrogen and progesterone receptors <10% and negative HER2 immunohistochemical staining) and overexpressed HER2 (HER2 immunohistochemical staining +++ or ++ and amplified in situ hybridization).

Data were collected from patients diagnosed in 2014 and 2015 to have data also on postoperative treatments and follow-up. The absence or presence of treatments such as chemotherapy, radiotherapy and hormonotherapy were collected. We also looked for local, regional, and distant relapses, and if the patient had died and on what date.

Axillary examination, lymph node surgery and histological analysis

Each patient had bilateral mammography and breast ultrasound at the time of initial management. An AUS was performed systematically during the initial workup. These investigations were carried out by four expert radiologists. A lymph node was classified as suspect in case of increased lymph node size, cortical thickening (>3 mm), cortical hypo echogenicity or loss of fatty hilum and the AUS result was given as positive.

All patients with an axillary node suspected of a secondary location had a FNAC using a 21G fine needle. The FNAC result was qualified as positive when lymph node cytology was found to have metastatic involvement. In these cases, ALND was performed; otherwise, the patient was eligible for a SLNB. The presence of isolated tumor cells (i+) in the axilla was considered as negative (N0).

Except when there were axillary lesions (N+), an ALND was performed without SLNB procedure in cases of multifocality (when 2 tumor foci were more than 5 cm apart), multicentricity (2 foci located in 2 different quadrants or when there were more than 2 foci) after validation in a multidisciplinary meeting.

The patients in our study did not benefit from it, but since 2022, it is possible to avoid ALND if the ACOSOG criteria are met in French recommendations [5,8]. They are defined as:

- The possibility of performing a SLNB if there is the presence of a single suspicious node on ultrasound and positive FNAC for

cT1-T2, cN0 tumors, in case of conservative surgical treatment and associated systemic adjuvant therapy.

- The possibility of not performing additional ALND in the case of a SLNB finding 1 or 2 macrometastatic nodes without capsular invasion, in cT1-T2, cN0 tumors that have benefited from conservative surgical treatment and where systemic adjuvant treatment is indicated.

The Overall Survival (OS) was evaluated from the date of surgery to the date of death or last follow-up, and reported at three and five years. The Progression Free Survival (PFS) was evaluated from the date of surgery to the date of documented disease progression or recurrence assessed on cross-sectional imaging.

Statistical analysis

Quantitative parameters were described as mean and standard deviation or by median and Interquartile Range (IQR) and qualitative parameters as frequency and percentage. Patients' characteristics at surgery were compared between the two groups with paired sample Student t-test or paired sample Wilcoxon test or Mac Nemar test in order to take into account the matching and paired differences were computed. Multivariate logistic regression was performed for each prognostic factor and parameters with a p value of less than 0.1 were introduced in a multivariate logistic regression with backward selection. Results were expressed as the odds ratio and 95% confidence. Interval OS and PFS were described by the Kaplan Meier method and compared by univariate Cox. For multivariate analysis, the primary outcome chose, was axillary burden. High axillary burden was defined by more than 3 positive lymph nodes. Significance level was set at 5%. The analyses were performed with STATA software version 14.0 (Stata Corp, College Statio, TX, USA).

Results

205 patients were initially included in this study. 4 patients were excluded because of lack of data on axillary ultrasound. 89 patients had no suspicious adenopathy clinically or by ultrasound. Of these, 4 were excluded for first ALND. 112 patients underwent FNAC for suspicious lymph nodes. Of these, 95 received an ALND because of the pathological nature of the FNAC, 14 received a SLNB because the FNAC was negative, and 3 were excluded because they received a primary ALND despite a negative axillary FNAC. These data are shown in the flowchart (Figure 1).

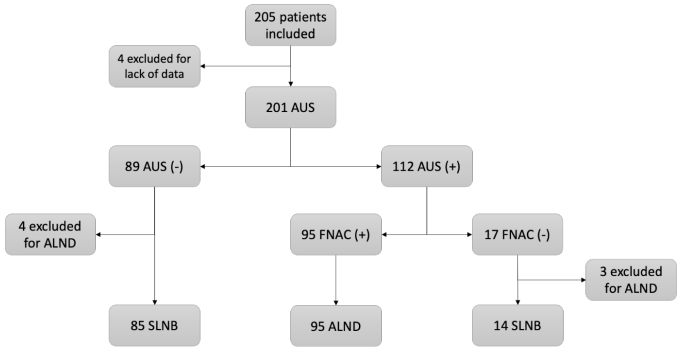


Figure 1: Flowchart of axillary lymph node treatment.

AUS: Axillary Ultrasound; SLNB: Sentinel Lymph Node Biopsy; ALND: Axillary Lymph Node Dissection; FNAC: Fine-Needle Aspiration Cytology.

Table 1 details the demographic, clinical and surgical characteristics. 99 patients were included in the Group 1. 95 patients were included in the Group 2. Patients in Group 1 were significantly younger, with a mean age at diagnosis of 57.9 years, compared with the Group 2 with a mean age of 62.5 years (p=0.011). The body mass index was also significantly higher in the Group 2 than in Group 1 with a mean BMI of 27.7 kg/m^2 vs. 26.01 kg/m^2 (p= 0.0440).

There was a significant difference in clinical tumor size between the two groups (p=0.005). Indeed 37.2% of the tumors were not palpable in Group 1, against 20.5% in the Group 2. 41% of the tumors were <2 cm in Group 1 versus 35% in Group 2 while 20.5% of the tumors were between 2 and 5 cm in Group 1 versus 37.6% in Group 2. Also, for T3 tumors with 1.3% for Group 1 versus 6.8% for Group 2. There was also a significant difference in mean size between the two groups on ultrasound, with a tumor size of 13.7 mm for Group 1 versus 22.7 mm for Group 2 (p<0.001).

The cN status shows a significant difference since 29.9% of the patients in Group 2 have at least one palpable adenopathy compared to Group 1 which represents 5.1% (p<0.001).

Table 1: Demographic, clinical and surgical characteristics.

	Group 1 (n=99)	Group 2 (n=95)	p-Value
Age (mean, SD) (years)	57.86(1.26)	62.49(1.21)	0.011
Body mass index (mean, SD) (kg/m^2)	26.06(5.05)	27.69(5.75)	0.044
BMI > 25 kg/m^2	56.41%	63.25%	0.339
Personal history of cancer	11.1%	10.4%	0.986
Right breast	46.15%	60.44 %	0.248
cT stage			0.005
cT0	37.18%	20.51%	
cT1	41.03%	35.04%	
cT2	20.51 %	37.61 %	
cT3	1.28%	6.84 %	
Localization			0.212
Outer quadrants	65.38%	72.65%	
Inner quadrants	28.21%	22.22%	
Central	6.41%	5.13 %	
cN stage			<0.001
cN0	94.87%	70.09 %	
cN1	5.13 %	29.91%	
BRCA mutation	1.28 %	2.56 %	0.536
Multifocality in the breast	12.82%	25.64%	0.030
ACR classification			<0.001
3	7.69%	4.27%	
4	34.62%	21.37%	
5	57.69 %	74.36 %	
Tumoral size in echography (mean, SD) (mm)	13.85 (6.63)	20.58 (11.58)	<0.001
Breast-conserving surgery	87.18 %	47.86 %	<0.001
Total mastectomy	12.82 %	52.14 %	<0.001

SD: standard deviation, cT clinical tumor size classification, cN clinical node presence classification, ACR American College of Radiology.

Laterality, quadrant, personal history of cancer, or BRCA mutation did not show significant differences between the two groups. Patients had more multifocal breast cancers in Group 2 than in Group 1(25.6% vs 12.8%) (p=0.030).

In Group 2, the majority of patients were treated by total mastectomy (52.14%) in contrast to Group 1(12.82%) (p<0.001).

Final histological characteristic

Concerning the histological results (Table 2), there was no significant difference in the histological type between the two groups (p=0.453). Invasive ductal carcinoma represented the majority of lesions found (about 80% in both groups).

There was a difference in terms of histological grade (p<0.001), with a majority of grade 2 in Group 1 (53.85% vs 43.59%) and more grade 3 in Group 2 (47.86%) compared to the GS group (17.95%).

Ki67 also differed between the two groups (p<0.001): 21.79% of the tumors in Group 1 had a Ki67<10% versus 11.11% for Group 2, between 10 and 30% were found in 67.95% of

the tumors in Group 1 and 52.14% in Group 2. There are more tumors with a Ki>30% in Group 2 than in Group 1 (36.75% vs 10.26%).

5.13% of tumors in Group 1 did not have estrogen receptors, compared to 14.53% in Group 2 (p=0.038). 17.95% of tumors in Group 1 did not have progesterone receptors, compared to 32.48% in Group 2 (p=0.025). There was a higher HER2 overexpression in Group 2 than in Group 1 but without significant difference (16.24% vs. 7.69%) (p=0.080). There was no significant difference for triple-negative tumors or in biomolecular classification (p=0.232).

There was also a difference in pT stage with 69.23% of pT1 cancer in Group 1 versus 40.17% in Group 2, 30.77% of pT2 cancer in Group 1 versus 51.28% in Group 2. We find 8.55% of pT3 cancer in Group 2. This difference was also found in the mean size of the lesion, with a significantly larger size in Group 2 (27.46 mm) compared to Group 1 (17.15 mm) (p<0.001).

Axillary involvement

As shown in Table 3, at the axillary level, there was an average of 18 nodes in Group 2 and 14 in the Group 1 (p<0.0006). There was an average of 2.2 positive nodes in Group 1, compared with 5.1 in Group 2 (p<0.001). There were more than 3 positive nodes in 54.70% of cases in Group 2 versus 21.70% in Group 1 (p<0.001). Group 2 also had more capsular effraction (69.23%) than Group 1 (30.77%).

In both groups, only macrometastases were found in the ALND. 78.78% of the patients in Group 1 had no other positive nodes in the ALND. The axillary tumor size was larger in Group 2 with an average of 16.89 mm compared to an average of 11.27 mm in Group 1.

The pN stage differed significantly with 91% of pN1 in Group 1, compared to 55.6% in Group 2 (p<0,001). While only 9% of pN2 and pN3 stage was found in Group 1, 44.4% of pN2 and pN3 stage was found in Group 2.

Table 2: Final histological characteristics:

	Group 1 (n=99)	Group 2 (n=95)	p-Value
Size of infiltrative lesions (mean, SD) (mm)	17.15 (7.29)	27.46 (20.95)	<0.001
Tumor localization			0.212
Outer quadrants	58.59%	69.81%	
Inner quadrants	27.27%	19.81%	
Central	12.12%	10.38%	
Multifocality	18.31%	25.97%	0.214
Histological type			0.453
Invasive ductal carcinoma	78.21%	82.05 %	
Invasive lobular carcinoma	14.10%	8.55 %	
Other	7.69 %	9.40 %	
LVSI	30.77%	46.15 %	0.032
Final histological grade			<0.001
1	28.21 %	8.55%	
2	53.85 %	43.59 %	
3	17.95%	47.86%	
Ki-67 rate (%)			<0.001
<10	21.79 %	11.11 %	
10-30	67.95%	52.14 %	
>30	10.26 %	36.75%	
ER negative status	5.13%	14.53%	0.038
PR negative status	17.95 %	32.48%	0.025
Overexpression of HER2	7.69%	16.24%	0.080
Triple negative	3.85%	7.69%	0.121
Biomolecular classification			0.232
Luminal A	82.05%	66.67 %	
Luminal B	6.41 %	9.40 %	
Overexpressed HER2	7.69 %	16.24%	
pT stage			<0.001
pT1	69.23%	40.17%	
pT2	30.77%	51.28%	
pT3	0%	8.55%	

SD: standard deviation; LVSI: lymphovascular space invasion; ER: estrogen receptor; PR: progesterone receptor; pT: histologic tumoral classification.

Multivariate analysis shown that only age at diagnosis (RR 2.79 [1.27; 5.74]), ultrasound tumor size (RR 2.97 [1.20; 7.64]), LVIS (RR 1.88 [1.07; 2.74]), multifocality (RR 2.27[1.35; 5.41]) and high histological grade (RR 3.38 [1.45; 9.74]) were significantly associated with a high axillary involvement.

Table 3: Axillary involvement

	Group 1 (n=99)	Group 2 (n=95)	p-Value
Number of positive nodes (mean, SD)	2.21 (0.26)	5.14 (0.26)	0.0001
>3 positive nodes	21.79%	54.70%	<0.001
Number of axillary nodes (mean, SD)	14.82 (0.71)	18.14 (0.62)	0.0006
Extracapsular effraction	30.77 %	69.23 %	<0.001
Size of axillary tumor (Mean, SD) (mm)	11.27 (0.84)	16.89(0.90)	<0.001
pN stage			<0.001
pN1	91.03%	55.56%	
pN2+3	8.97%	44.44%	
ACOSOG [(1)]	60.26%	27.35%	<0.001
Post-operative chemotherapy	53.85%	73.50%	0.005

SD: standard deviation; pN: histologic node classification; ACOSOG: Alliance for Clinical Trials in Oncology.
[(1)]Rate of patients who would not have received ALND according to ACOSOG criteria.

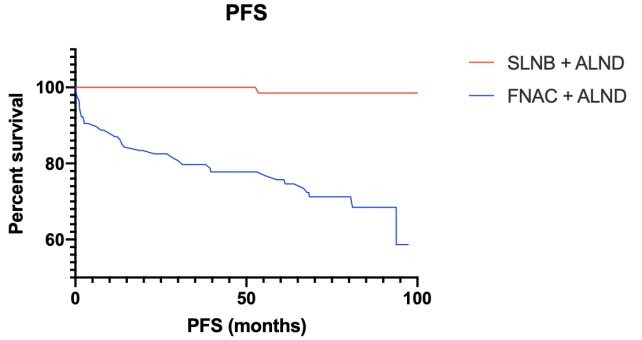
ACOSOG

According to the ACOSOG criteria and the 2022 French recommendations, in this study, 60.26% of patients in group 1 would not have had ALND and 27.35% in group 2 would have been treated by SLNB.

Adjuvant treatment and survival

In Group 1, 53.85% of patients received postoperative chemotherapy compared to 73.50% in Group 2 (p=0.005). There was no difference in treatment with radiotherapy and hormone therapy between the two groups.

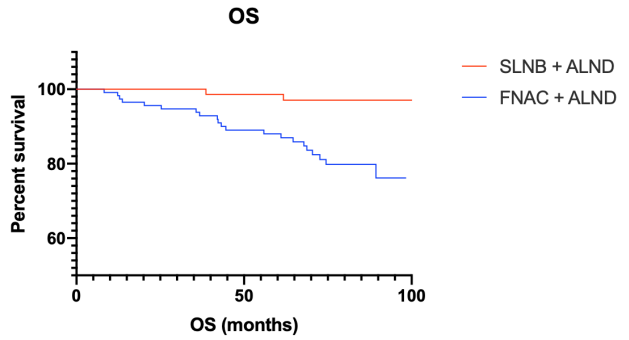
There was a significant difference in progression-free survival between the two groups (Graph 1). Indeed, there was a 1.28% recurrence rate at 5 years in Group 1, compared with 28.21% recurrence rate at 5 years in Group 2 (p<0.001). There was also a significant difference in overall survival between the two groups (Graph 2)). Overall survival at 5 years was 97.44% in Group 1 versus 82.05% in Group 2 (p=0.001).



Graph 1: Progression-free Survival (p-Value<0,001).

5-year recurrence rate: (SLNB+ ALND): 1.28%, (FNAC + ALND) : 28.21% (p<0,001).

PFS: Progression Free Survival; SLNB: Sentinel Lymph Node biopsy; ALND: Axillary Lymph Node Dissection; FNAC: Fine Needle Aspiration Cytology.



Graph 2: Overall survival (p-Value<0,0018).

5-year survival rate: Group 1: 97.44%, Group 2: 82.05 (p= 0,001).

OS: Overall Survival; SLNB: Sentinel Lymph Node Biopsy; ALND: Axillary Lymph Node Dissection; FNAC: Fine Needle Aspiration Cytology.

Discussion

Axillary involvement in breast cancer is a major prognostic factor. Indeed, the 5-year overall survival rate for patients with cancer without axillary involvement is 98.8% and drops to 85.8% for patients with lymph node involvement [3,11].

Our study shown that patients with preoperative positive fine needle biopsy have a greater degree of lymph node involvement and a worse overall and progression-free survival than patients whose lymph node involvement was discovered at the time of the SLNB.

In our study, we shown that higher age is a risk factor for lymph node invasion. Nevertheless, there is a discrepancy with several articles that find, for Ding et al. [12] and Moosavi et al. [13], that younger age is more often associated with aggressive cancers and with a higher risk of lymph node invasion, and Xie et al. [14] that find similarities with our work, with a higher rate of lymph node invasion in older patients.

On the radiological evaluation, it has also been noted that the larger the tumor on ultrasound, the greater the risk of lymph node invasion. Ding et al. [12], Moosavi et al. [13], Malter et al. [15], Mohammed et al. [16] and Costa et al. [17], comparing patients with and without axillary involvement, also show that tumor size is a risk factor for lymph node involvement in breast cancer. In our study, we shown that beyond the risk of lymph node invasion, tumor size is also a risk factor for the rate of lymph node invasion.

At the histological level, we noted that the presence of lymphovascular invasion is also a risk factor for the rate of lymph node invasion, with a higher number of lymph nodes affected. Moosavi et al. [13], Malter et al. [15] and Costa et al. [17] find data similar to our work, namely that lymphovascular invasion of the breast tumor has an impact on the risk of lymph node invasion.

It is highlighted that a high histological grade is also a risk factor for the rate of lymph node invasion. Ding et al. found results [12] similar to ours.

Regarding multifocal character, many previous studies, as Boros et al. [18] and Coombs et al. [19] have shown that multiple breast carcinomas are associated with a higher risk of axillary

lymph node metastases, our study goes further by finding that multifocal character will also be associated with a higher rate of lymph node invasion in affected patients.

Orsaria et al. [20] suggests that, progesterone and estrogen receptors and HER2, as the main risk factors for lymph node invasion, differ with age and will have an effect on tumor size. This would imply that it is not directly age or tumor size that would be predictive of lymph node invasion but rather these three factors: ER, PR and HER2 status. In our study, although in univariate analysis, these hormonal factors and HER2 status appear to be risk factors for lymph node invasion, these factors are not significantly different between the two groups in multivariate analysis.

Verheuvel et al. [21] and Farrel et al. [22] showed that a positive preoperative axillary ultrasound has a worse prognosis and is a risk factor for greater lymph node invasion than in the event of discovery of lymph node invasion on the SLNB. Our study is consistent with these results since there is a worse lymph node invasion in group 2.

Our study has some limitations as it is a single-center, retrospective study with a limited number of inclusions and without randomization, which limits its efficiency. Nevertheless, all these data came from patients treated in an expert center, with a homogeneity of the examinations at the time of diagnosis and management. In addition, the two compared groups belong to patient populations with axillary involvement, so it is difficult to extrapolate our results to patients with node-negative breast cancer patients.

However, there are few studies that studying the risk and predictive factors for the degree of lymph node invasion in patients with axillary involvement, which makes our article relevant. Moreover, our study shows that 54% of patients with suspected adenopathy with positive FNB had more than 3 lymph nodes affected during the ALND. This suggests caution in performing a SLNB in patients with a "single" node invasion on FNB according to the ACOSOG criteria. Nevertheless, due to the retrospective nature of the data collected, the number of suspicious nodes on ultrasound is not well described. Indeed in 2014 and 2015, as the ACOSOG criteria were not yet applied, the pertinence of knowing the number of suspicious nodes was reduced. This limits us in knowing what proportion of patients, who had a positive FNB and then an ALND in our study, could have had a SLNB and would have been underestimated.

However, the role of ALND is increasingly disputed. As noted in our study, a majority of patients with positive nodes found by SLNB have no other nodes affected by ALND. Furthermore, with the improvement of adjuvant treatments, the rate of axillary recurrence remains low in patients who have not benefited from a positive SLNB, without ALND [23]. Our results are an additional argument in the therapeutic decrease of ALND.

Conclusion

In conclusion, our study has shown that age, tumor size (on ultrasound), lymphovascular invasion, multifocality and histological grade are risk and predictors factors of the rate of lymph node invasion. These results could, if confirmed in a new prospective study, eventually allow patients with affected SLNB but belonging to a low-risk group, to avoid ALND and thus complement the already known ACOSOG Z0011 and French recommendations criteria.

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Ethical approval: According to French regulation, patients were informed of the researches performed and did not express opposition. The study was authorized by the Internal Scientific Committee and

Ethical Board of the Institut de Cancérologie de Lorraine (05-2019).

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