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Axillary lymph node micrometastases decrease triple-negative early breast cancer survival

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Background: Triple-negative breast cancers (TNBCs) are the most deadly form of breast cancer (BC) subtypes. Axillary lymph node involvement (ALNI) has been described to be prognostic in BC taken as a whole, but its prognostic value in each subtype is unclear. We explored the prognostic impact of ALNI and especially of small size axillary metastases in early TNBCs.

Methods: We analysed in this multicentre study all patients treated for early TNBC in 12 French cancer centres. We explored the correlation between clinicopathological data and ALNI, with a specific focus on the dichotomisation between macrometastases and occult metastases, which is defined as the presence of isolated tumour cells or micrometastases. The prognostic value of ALNI both in terms of disease-free survival (DFS) and overall survival (OS) was also explored.

Results: We included 1237 TNBC patients. Five-year DFS and OS were 83.7% and 88.5%, respectively. The identified independent prognostic features for DFS were tumour size >20 mm (hazard ratio (HR) $=1.86$; 95% CI: 1.11–3.10, $P=0.018$), lymphovascular invasion (HR $=1.69$; 95% CI: 1.21–2.34, $P=0.002$) and ALNI both in case of macrometastases (HR $=1.97$; 95% CI: 1.38–2.81, $P<0.0001$) and occult metastases (HR $=1.72$; 95% CI: 1.1–2.71, $P=0.019$). DFS and OS were similar between tumours with occult metastases and macrometastases. Tumours presenting at least two pejorative features (out of ALNI, lymphovascular invasion and large tumour size) displayed a significantly poorer DFS in both the training set and validation set, independently of chemotherapy administration. Tumours with no more than one of the above-cited pejorative features had a 5-year OS of $\geqslant 90\%$ *vs* 70% for other cases ($P<0.0001$).

Conclusions: Axillary lymph node involvement is a key prognostic feature for early TNBC when isolated tumour cells were identified in lymph nodes. This impact is independent of chemotherapy use.

Since the early 2000s gene expression profiling analyses have markedly improved breast cancer (BC) understanding by defining BC molecular subtypes (Perou *et al*, 2000). Even though it represents only a partial view of BC biological heterogeneity, their

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use in clinical routine practice is surrogated by the immunohistochemical assessment of hormone receptors (HRs) and HER2 expression.

Triple-negative breast cancers (TNBCs) are defined by a lack of expression of the oestrogen receptor (ER), the progesterone receptor (PR) and the absence of HER2 protein overexpression or gene amplification. They represent 15–25% of all BCs (Rakha and Ellis, 2009) and nearly 75% of them are included in the basal-like molecular subtype (Bertucci *et al*, 2008; Gonçalves *et al*, 2013). Most of the *BRCA1*-mutated patients develop TNBCs, and *BRCA1*-wild-type TNBCs share molecular similarities with *BRCA1*-mutated tumours (Robertson *et al*, 2012; Schmadeka *et al*, 2014) TNBCs display some clinical and pathologic specificities, better response rates to chemotherapy but higher rates of local relapses and poorer prognosis (Liedtke *et al*, 2008; Dawson *et al*, 2009; Foulkes *et al*, 2010; von Minckwitz *et al*, 2014). They relapse earlier than HR-positive BC with more visceral metastases (Liedtke *et al*, 2008; Foulkes *et al*, 2010). Triple-negative breast cancer management is currently based on cytotoxic chemotherapy (Jacquin *et al*, 2012; Mackey *et al*, 2013). As TNBCs demonstrate poor prognosis, efforts are needed to identify better prognostic and predictive markers to improve TNBC management.

Axillary lymph node involvement (ALNI) is known to be a major BC prognostic feature for decades (Fisher *et al*, 1983). Even though ALNI cannot be precisely predicted by molecular subtype classifications (Howland *et al*, 2013; Jones *et al*, 2013), its incidence seems to be lower in luminal A and higher in HER2-positive tumours (Park *et al*, 2012; Howland *et al*, 2013). It is moreover a key factor to determine the need of adjuvant chemotherapy. Assessment of a few nodes by sentinel lymph node biopsy (SLNB) can identify small size involvements such as isolated tumour cells (ITCs, <0.2 mm) or micrometastases (<2 mm). Because of improvements in pathological techniques with serial sections and immunohistochemistry (IHC) examination, a better identification of ALNI has been observed (Houvenaeghel *et al*, 2006).

This multicentre retrospective study aimed to identify prognostic factors in early TNBCs, with a focus on the prognostic value of the type of ALNI (occult metastases or macrometastases).

MATERIALS AND METHODS

In this retrospective, multicentre cohort study, we analysed data from women with primary TNBCs treated in 12 French centres between 1987 and 2011. This work was approved by our institutional ethics committee and *Société Française de Chirurgie Oncologique*.

Patients' inclusion criteria. Patients with first-line treatment for early-stage invasive BC without metastasis at diagnosis and with no expression of ER, PR ($<10\%$ of cancer cells expressing ER/PR, as defined in the French guidelines) or ERBB2 identified by IHC (score 0 or 1) were included. For cases with an IHC score of 2, we looked for HER2 amplification using *in situ* hybridisation technologies (Penault-Llorca *et al*, 2014). Exclusion criteria were clinical T4, bilateral disease, neoadjuvant treatment and any personal history of cancer.

Data collection. After obtaining approval from our institutional ethics committee, data were collected from individual medical files. Information gathered included demographic (age at diagnosis), clinical (cTNM), pathological (pathological subtype, tumour grade determined by the Scarff–Bloom–Richardson scoring system, pathological tumour size, presence of lymphovascular invasion (LVI) assessed by haematoxylin and eosin staining, axillary lymph node status (ITC, micrometastasis or macrometastasis)) and therapeutic data (type of surgery, adjuvant chemotherapy).

Axillary lymph node involvement assessment was performed using either SLNB after radioisotope and/or blue dye injection, or axillary lymph node dissection (ALND). We defined five groups: no lymph node metastasis (pN0), ITC (<0.2 mm; pN0(i+)), micrometastases (<2 mm; pN1mic), isolated macrometastasis (≥ 2 mm, pN1) and multiple macrometastases. Isolated tumour cells and micrometastases were assessed using serial sections and IHC examination (Houvenaeghel *et al*, 2006).

Survival analysis. Follow-up was measured from the date of diagnosis to the date of last news for living patients. All patients were followed up in their tertiary cancer centre or out of these centres in collaboration with their GP or local oncologist. Patients were censored when these follow-ups could not be performed with a minimal follow-up duration of 1 year. Overall survival (OS) and disease-free survival (DFS) were defined as the time from diagnosis to death from any cause or relapse.

Statistical analysis. Axillary lymph node involvement prognostic value had been adjusted to age, tumour size, pathological grade, pathological subtype and LVI. The prognostic impact of above-cited factors was assessed by the Cox regression method in univariate analysis and *P*-values were estimated with the Wald test. Only factors with a *P*-value $\leqslant 0.05$ in univariate analysis were kept for multivariate analysis.

We compared the use of adjuvant chemotherapy according to clinicopathological features including ALNI status.

We developed a score to predict DFS, according to the hazard ratios (HRs) from the Cox model in a training set representing two-thirds of our cohort ($n=825$). We looked at the presence of 0–3 risk factors resulting in a score of 0–3 for each sample. We then validated this score using a validation set including the last third of our cohort ($n=412$). We chose to split our cohort because no external cohort with appropriate clinicopathological individual data was available. To define both the training and validation sets, we classified all the cases according to their age in an ascending order: the first two patients were included in the training set and the third in the validation set. Survival analyses were performed separately in the training and validation sets.

Data concerning patients without disease progression or death at last follow-up were censored. Survival curves were estimated using the Kaplan–Meier method, and compared with the log-rank test. The Pearson's χ^2 test was used to compare descriptive items.

All statistical tests were two sided at the 5% level of significance and analyses were performed using the SPSS 16.0 software for Windows (SPSS Inc., Chicago, IL, USA).This work was carried out according to the Strengthening the Reporting of Observational Studies in Epidemiology criteria (Vandenbroucke *et al*, 2007).

RESULTS

Patient's characteristics. We collected data from 1237 patients with a primary early-stage TNBC. The main patient characteristics are summarised in Table 1. The mean age of the patients at diagnosis was 55.7 years old (95% CI: 55–56.4; median = 56) and the mean tumour size was 20.8 mm (95% CI: 19.9–21.7; median = 17).

Axillary lymph node dissection was performed for 588 patients (47.6%) and 889 (71.9%) underwent initial SLNB including 244 with a secondary ALND. Less than a quarter (22.8%) of our patients presented an ALNI including 35 patients (2.8%) with pN0(i+), 55 (4.5%) with pN1mic and 191 (15.5%) with pN1. Out of pN1 cases, 39.8% (68 out the 171 cases with data available) had only one ALNI and 60.2% (103/171) had two or more ALNI. When an SLNB was performed, one or more non-sentinel metastatic lymph nodes were identified for 0.8% (5/643), 0% (0/15), 17% (8/47) and 49.3% (38/77) of negative, ITC, micrometastatic and

Table 1. Clinicopathological features

	N	%
Age (years)		
⩽40	157	12.7
41–50	273	22.1
51–65	531	43
66–75	210	17
>75	64	5.2
Clinical tumour size (cT)		
T0	213	17.3
T1	675	54.7
T2	310	25.1
T3	36	2.9
Unknown	3	
Pathological tumour size (mm)		
0–5	76	6.2
5.1–10	190	15.4
10.1–20	549	44.6
20.1–30	243	19.8
>30	172	14
Pathological subtype		
Ductal	1051	85
Lobular	58	4.7
Mixed	5	0.4
Medullary	42	3.4
Others	81	6.5
Tumour grade		
1	95	7.7
2	291	23.5
3	822	66.5
Unknown	29	2.3
LVI		
No	848	68.6
Yes	277	22.4
Unknown	112	9
Pathological ALN status		
pN0	951	77.2
pN0(i+)	35	2.8
pN1mic	55	4.5
pN1	191	15.5
Metastatic evolution		
No	1089	88
Yes	148	12
Breast surgical resection		
Conservative	613	81
Mastectomy	144	19
SLN biopsy		
No	348	28.1
Yes	889	71.9
ALN dissection		
No	648	52.4
Yes	588	47.6
Adjuvant chemotherapy		
No	288	23.3
Yes	949	76.7

Abbreviations: ALN = axillary lymph node; LVI = lymphovascular invasion; N = number of patients; pN = pathological lymph onde involvement; SLN = sentinel lymph node.

macrometastatic SLNs, respectively. Most of the patients (76.7%) received adjuvant chemotherapy.

Disease-free survival. Median follow-up was 52.8 months. We observed 190 (15.4%) recurrences including 148 (12%) distant metastases and 139 (11.2%) deaths. Five-year DFS was 83.7% in the whole cohort.

Univariate analysis of disease-free survival showed that tumour size, LVI, high grade and ALNI were significant prognostic factors (Table 2 and Figure 1). Disease-free survival was significantly longer for pN0 cases *vs* (pN0(i+)/pN1mic) ($P=0.003$). No difference was observed between pN0(i+) and pN1mic ($P=0.262$), as well as between pN0(i+)/pN1mic and pN1 ($P=0.343$). Disease-free survival was longer for patients presenting only one lymph node macrometastasis ($n=68$) *vs* more than one macrometastasis ($n=103$) ($P=0.019$).

Only tumour size ⩾20 mm (HR = 1.86; 95 CI%: 1.11–3.09; $P=0.018$), LVI (HR = 1.69; 95 CI%: 1.21–2.34; $P=0.002$) and ALNI were still significant in multivariate analysis. Axillary lymph node involvement prognostic value was observed for both pN0(i+)/pN1mic (HR = 1.72; 95 CI%: 1.1–2.71; $P=0.019$) and macrometastases (HR = 1.97; 95 CI%: 1.38–2.81; $P<0.0001$). After adjusting for chemotherapy administration, all these features remained significant (Supplementary Table 1). Furthermore, DFS was significantly lower for TNBCs with two or more macrometastases (HR = 2.55; 95 CI%: 1.66–3.92; $P<0.0001$).

A prognostic score is able to predict DFS. To better appreciate the risk of disease recurrence, we defined a score including variables harbouring a significant prognostic value in multivariate analysis. Each of these features were noted as 0 (pT⩽20 mm, pN0, no LVI) or 1 (pT>20 mm, pN0(i+)/pN1mic/pN1, presence of LVI). A score of 0–3 was thus attributed to all patients of the training set and then validated on 412 independent samples. Clinicopathological features (age, pathological subtype, grade, LVI, tumour size, ALNI, chemotherapy administration's rate) were similar in both sets. In the training set, HR for disease recurrence were 2.5 (95 CI%: 1.69–3.70; $P<0.0001$), 1.6 (95 CI%: 1.05–2.4; $P=0.029$), 1.98 (95 CI%: 1.12–3.51; $P=0.019$) and 1.89 (95 CI%: 1.19–3.01; $P=0.007$) for pT>20 mm, LVI, pN0(i+)/pN1mic and pN1, respectively.

Our prognostic score displayed a significant prognostic value both in the training and validation sets (Figure 2). This prognostic value was independent of the use of adjuvant chemotherapy for patients presenting 0, 1 or 2 prognostic factors. For patients with three pejorative features, even though this was a small size group, chemotherapy improved survival ($P=0.009$). In the validation set, 5-year DFS was significantly longer for patients with a score of 0 (87.7%) than for patients with 1 (82.6%), 2 (76.5%) and 3 (44.6%) pejorative features (Supplementary Table 2).

Overall survival. Five-year OS was 88.5% for the whole cohort. Univariate analysis of overall survival showed that age, tumour size, grade, LVI and ALNI were prognostic ($P<0.0001$ for all). They all kept their prognostic value in multivariate analysis: age over 75 years (HR = 5.46; 95 CI%: 2.50–11.9; $P<0.0001$), tumour size >20 mm (HR = 2.05; 95 CI%: 1.42–2.95; $P<0.0001$), LVI (HR = 1.76; 95 CI%: 1.21–2.55; $P=0.003$), tumour grade (3 *vs* 1–2; HR = 1.67; 95 CI%: 1.10–2.55; $P=0.017$)and pN1 ALNI (HR = 1.78; 95 CI%: 1.15–2.74; $P=0.009$). No difference could be observed between pN0(i+)/pN1mic and pN1 cases ($P=0.606$). Moreover, OS was significantly lower for TNBCs with two or more macrometastases (HR = 2.01; 95 CI%: 1.22–3.32). Because chemotherapy indication is based on the presence of poor prognostic features, administration of adjuvant chemotherapy was correlated with a worst prognosis (chemotherapy *vs* no chemotherapy: HR = 1.85; 95 CI%: 1.12–3.06; $P=0.016$). After adjusting for chemotherapy administration, all clinicopathological features remained significant (Supplementary Table 1).

We then assessed the capacity of our prognostic score to predict OS. Overall survival was significantly different across the four groups ($P<0.0001$) (Figure 3). Patients with a score of 0–1 had a 5-year OS of 93.5% and 90.9%, respectively, whereas patients with a score ⩾2 had significantly poorer 5-year OS of 74.6% and 68.8%, respectively (Supplementary Table 3). It is worth noting that

OS was influenced by adjuvant chemotherapy administration, with a longer survival for patients presenting 0–2 pejorative prognostic features when they receive chemotherapy ($P = 0.004$). Despite a few patients with a score of 3 did not receive chemotherapy, systemic chemotherapy also significantly improved survival in this subset ($P = 0.013$).

Table 2. Disease-free survival and overall survival results: univariate and multivariate analysis

	Disease-free survival			Overall survival		
	Log rank *P*-value	Cox[a] *P*-value	HR (95% CI)	Log rank *P*-value	Cox[a] *P*-value	HR (95% CI)
Age (years)						
⩽40	0.073			<0.0001		1
41–75					0.083	1.62 (0.94–2.81)
>75					**<0.0001**	5.46 (2.50–11.9)
pT (mm)						
0–10	<0.0001		1	<0.0001		1
>20		**<0.0001**	1.96 (1.44–2.66)		**<0.0001**	2.05 (1.42–2.95)
LVI						
Yes *vs* no	<0.0001	**0.001**	1.68 (1.22–2.32)	<0.0001	**0.003**	1.76 (1.21–2.55)
pN						
pN0	<0.0001		1	<0.0001		1
i+, mic		**0.019**	1.72 (1.1–2.71)		**0.121**	1.52 (0.89–2.59)
Macro		**<0.0001**	1.97 (1.38–2.81)		**0.009**	1.78 (1.15–2.74)
Grade						
3 *vs* 1 or 2	0.047	0.169		0.018	**0.017**	1.67 (1.10–2.55)
Chemotherapy						
No *vs* yes	0.622			0.744		
Pathological subtype	0.433			0.565		

Abbreviations: 95% CI = 95% confidence interval; HR = hazard ratio; LVI = lymphovascular invasion; N = number of patients; pN = pathological lymph onde involvement; pT = pathological tumour size.
[a]Wald test.

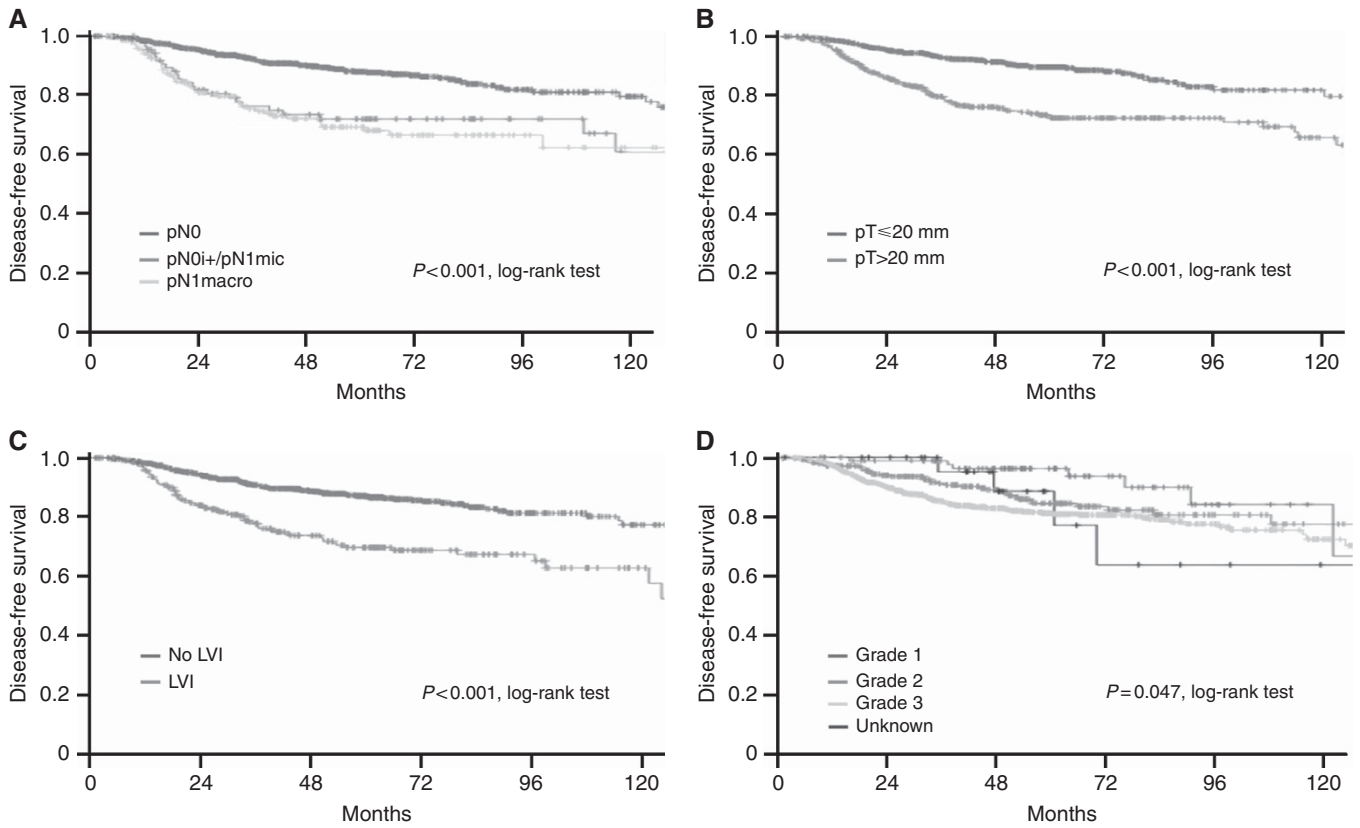

Figure 1. Disease-free survival according to prognostic factors. (**A**) axillary lymph node status, (**B**) tumour size, (**C**) presence of lymphovascular invasion (LVI), (**D**) tumour grade.

Clinicopathological features associated with ALNI. As LN involvement was an independent prognostic feature in our cohort, we decided to look for other pathological factors able to predict ALNI of any size (Table 3). Multivariate analysis showed that pathological features, such as tumour size (odds ratio (OR) = 1.97 for tumours 11–20 mm (95 CI%: 1.1–3.49; $P = 0.021$); OR = 4.29 for tumours >20 mm (95 CI%: 2.43–7.56; $P < 0.0001$) and LVI (OR = 4.17; [3.5–5.8]; $P < 0.0001$), correlated with ALNI. Comparison between ALN status, with distinction between pN0, pN0(i+), pN1mi and pN1, and the other pathological features is presented in Supplementary Table 4. Large tumour size, high grade and presence of LVI were more frequent in cases presenting ALNI. No significant difference could be identified between pN0(i+) and pN1mic tumours.

ALNI is used to prescribe systemic chemotherapy. As recommended by BC guidelines (Saint Gallen 2015), ⩽3 ALNI did not always require the use of chemotherapy. To determine if in clinical practice the choice to use chemotherapy was based more on tumour features than on LN status, we explored the clinicopathological features that correlated with chemotherapy administration. Predictive characteristics of chemotherapy use identified by univariate analysis were age, tumour size, LVI, tumour grade, pathological subtype and ALNI (Supplementary Table 5). All these features remained significant in multivariate analysis. With regard to ALNI, pN1 ($P = 0.002$) and pN1mic ($P = 0.004$) were significantly associated with chemotherapy use, whereas the presence of ITC was not ($P = 0.09$).

DISCUSSION

This study has included the largest cohort of TNBC with ALNI details ever published. Occult ALNI display an independent prognostic value that seems to be equal to that of the presence of one macrometastasis. Axillary lymph node involvement is moreover independent of all other usual clinicopathological features.

This study is the first work evaluating the prognostic value of the type of ALNI in early TNBC treated by front-line surgery. Some authors described that TNBC showed a significantly lower risk of ALNI than HR-positive or HER2-positive tumours (Holm-Rasmussen *et al*, 2015). We have previously explored the prognostic value of microscopic ALNI for 8001 BC patients with SLNB without molecular selection (Houvenaeghel *et al*, 2006). Only macrometastases were correlated with prognosis with an intermediate outcome for cases with one lesion and a poor outcome for tumours with at least two macrometastases. Occult metastases were not predictive of disease recurrence and death. However, published series showed discordant results. Six-year OS and 5-year DFS were similar between pN0 and pN0(i+)/pN1mic patients (Hansen *et al*, 2009; Maaskant-Braat *et al*, 2011). Others showed discrepant results with a poorer 10-year OS for patients with pN0(i+)/pN1mic ALNI (Truong *et al*, 2010; Weaver *et al*, 2011). Such a discrepancy in studies including all molecular subtypes may be explained by the fact that occult metastases may display heterogeneous prognostic values across molecular subtypes.

This study is the first to define the prognostic value of occult ALNI for TNBC. Axillary lymph node involvement was less frequent in TNBC compared with that in HER2-positive BC (Reyal *et al*, 2011; Houvenaeghel *et al*, 2014). In BC ⩽30 mm, ALNI was ⩽30% for TNBC *vs* ⩾50% for the other subtypes. In the current study, ALNI is correlated independently with tumour size >11 mm and LVI. We moreover show that occult metastases are independently associated with OS and DFS. They increase risks of disease recurrence and mortality by similar HR compared with the presence of one macrometastasis. However, this lack of statistical difference in prognosis may simply be a power issue owing to the relative small size of the ITC/mic+ group ($n = 90$). We are the first group to dichotomise TNBC patients with the presence of one or more macroscopic ALNI. Disease-free survival and OS are significantly lower for TNBCs with two or more LN macrometastases (HR = 2.55 and 2.01, respectively).

The other independent prognostic features identified were tumour size and LVI. Tumour size has been described to be correlated with BC prognostic for decades (Fisher *et al*, 1969; Carter *et al*, 1989; Neville *et al*, 1992). Its prognostic impact remains significant within each molecular subtype (Chia *et al*, 2004). The presence of LVI has

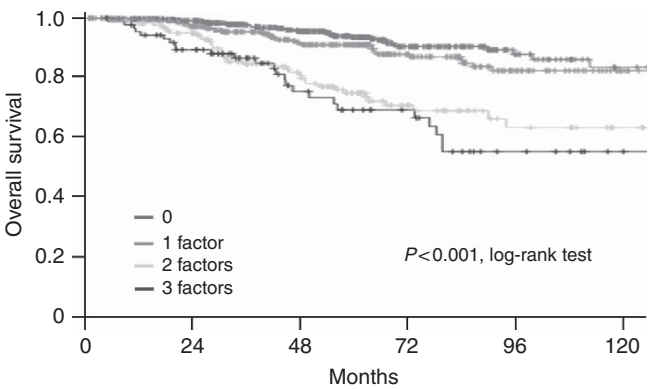

Figure 3. Overall survival according to prognostic score.

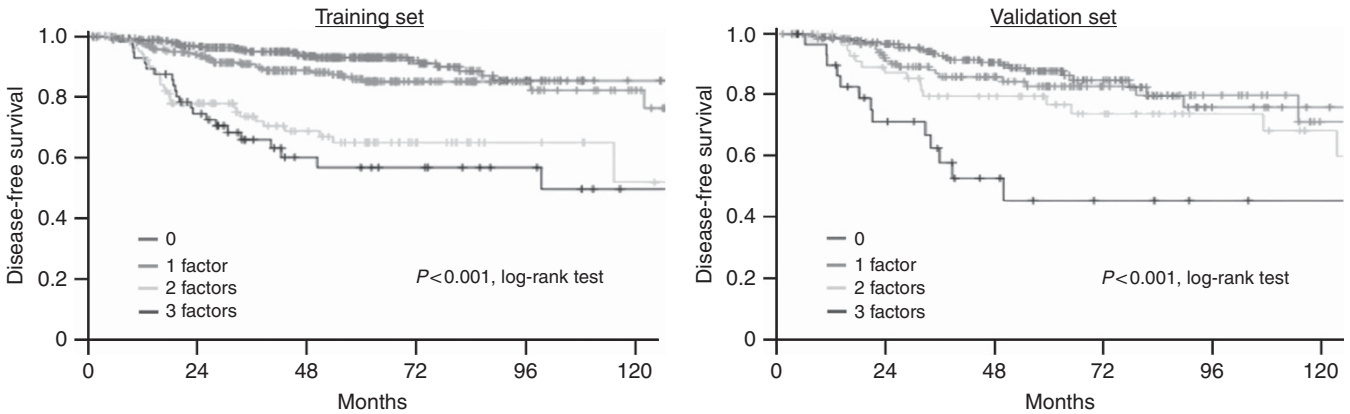

Figure 2. Disease-free survival according to prognostic score (0 to 3 factors) for Training set and Validation set.

Table 3. Clinicopathological features predictive of axillary lymph node involvement

	pN0		pN+			Cox multivariate analysis		
Predictive factors	Nb	%	Nb	%	Univariate analysis χ^2	*P*-value[a]	OR	95% CI
pT (mm)								
0–10	241	93.1	18	6.9	**<0.0001**		1	
11–20	437	79.9	110	20.1		**0.021**	**1.97**	1.1–3.49
>20	266	64.3	148	35.7		**<0.0001**	**4.29**	2.43–7.56
Age (years)								
⩽40	115	73.7	41	26.3	0.364			
41–75	784	77.5	228	22.5				
>75	51	82.3	11	17.7				
LVI								
No	715	84.6	130	15.4	**<0.0001**	**<0.0001**	1	
Yes	145	52.5	131	47.5			**4.17**	3–5.8
Grade								
1	86	90.5	9	9.5	**<0.0001**			
2	226	78.2	63	21.8		0.41		
3	612	74.6	208	25.4		0.53		
Unknown	27	96.4	1	3.6				
Histology								
Ductal	803	76.6	245	23.4	0.102			
Lobular	39	69.6	17	30.4				
Mixed	5	100	0					
Medullary	37	88.1	5	11.9				
Others	67	82.7	14	17.3				

Abbreviations: 95% CI = 95% confidence interval; LVI = lymphovascular invasion; N = number of patients; OR = odds ratio; pN = pathological lymph onde involvement; pT = pathological tumour size. Bold entries corresponds to stastistically significant results.
[a]Wald test.

also been described to be prognostic in BC for decades. LVI decreased DFS after adjustment for tumour size and ALNI (Bettelheim *et al*, 1984). LVI is known to be a major and independent prognostic feature in TNBCs with a three-fold increase in the risk of distant metastasis (Sabatier *et al*, 2011). In this study, we show that despite this prognostic value of LVI, ALNI and the type of ALNI are prognostic.

These results may lead to changes in systemic management of TNBCs. The choice to give adjuvant chemotherapy is currently mainly based on tumour features. However, in this study, we show that clinicians more often chose to administrate chemotherapy in patients with ALNI, independently of the size of these metastases and of tumour size and LVI. This observation has already been made by others who showed that BC patients with occult LNI received more chemotherapy than node-negative patients (Maaskant-Braat *et al*, 2011; Houvenaeghel *et al*, 2014).

To better identify patients with poor prognosis, we defined a prognostic score on a training set and validated it on the remaining patients. This score can be applied to all TNBCs. It is able to distinguish patients with significantly different prognoses, notably different OS. Patients with none or one pejorative feature had a 5-year OS of ⩾90%, whereas it was close to 70% for cases with two or three pejorative criteria. Further studies are thus warranted to decrease systemic therapy use for low score patients and/or to increase treatments for high score ones.

In this study, a complementary ALND were performed for patients with SN involved by ITC or micrometastases. In some centres, complementary ALND is not systematically performed since the reports of the results of the ACOSOG Z0011 and IBCSG 23-01 trials, but without consideration of molecular subtyping (Giuliano *et al*, 2010; Galimberti *et al*, 2013). By omitting to perform this complementary resection, 10–18% of patients with SN involved by ITC or micrometastases have non-sentinel node macrometastases that remain unknown. This should lead clinicians to make the choice to use systemic chemotherapy for TNBC patients presenting ITC or micrometastases as the only poor prognostic feature (Aigner *et al*, 2013).

This work has some limitations. The first one is its retrospective design. However, this can be counterbalanced by the fact it includes a large sample size. Adjuvant systemic therapies had not been standardised and chemotherapy details were not available for analysis. It is worth noting that ALND was performed for most of the patients in the early 1990s, whereas it is currently performed only for SLN-positive cases. Some ALNI could have been missed because of SLN-false-negative results (Layeequr Rahman *et al*, 2015). Finally, we chose to not analyse radiotherapy data here as they were missing for a large part of our cohort.

In conclusion, this study is the first to monitor the prognostic value of the type of lymph node involved in a large TNBC cohort. Axillary lymph node involvement is a key prognostic feature involved independently of its size. Occult metastases thus display a significant prognostic value in the TNBC population independent of other prognostic factors such as tumour size and LVI. Axillary lymph node involvement diagnosis thus seems to be crucial for TNBC, with the need to look for ITC and micrometastases by serial sections and IHC examination. This need may be importatn for small size tumours without other criteria of chemotherapy administration as it is for ER-positive cancers (Parmigiani *et al*, 1999). Prospective studies deserve to be performed to assess adjuvant chemotherapy benefits for early TNBC with occult ALNI.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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