Is sentinel lymph node biopsy alone accurate for breast cancer mastectomy? Results of a cohort study of 2423 patients.

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Abstract

Backgroud: Few patients with mastectomy and only with pN0(i+) or pN1mi sentinel node (SN) were included in randomized trial. To demonstrate SN biopsy accuracy for mastectomy. Methods: We examined results of SN among a multi-institutional cohort of patients, <=cT2-N0, who required total mastectomy, according to SN status and complementary axillary lymph-node dissection (cALND) or not. We have analyzed involved non-sentinel node (NSN) rate at cALND, overall (OS) and disease-free survival (DFS).

Results: Among 2423 patients we reported 1307 pN0(i-)SN, 120 pN0(i+)SN, 273 pN1miSN and 723 pN1macro-metastases SN with cALND respectively in 24.5, 73.3, 82.4 and 93.1%. Median follow-up was 42.72 months. Among 320 patients with pN0(i-)SN we observed 35 NSN macro-metastases (10.9%) and among 723 patients with SN macro-metastases, cALND was omitted in 50 patients (6.9%): in multivariate analysis, OS and DFS were not significantly different according to cALND or not. Among 120 patients with pN0(i+)SN and 273 with pN1miSN, cALND were respectively omitted in 32 and 48 patients: age, pT-size and SN-status were predictive of NSN involvement. In multivariate analysis, post-mastectomy radiotherapy, regional nodal irradiation and adjuvant chemotherapy were significantly correlated to cALND and a significant lesser DFS rate was reported for patients without cALND (HR: 3.861, p=0.002). Conclusion: SN biopsy appeared as an accurate procedure for axillary staging of breast cancer mastectomy for pN0 SN status. For pN1-macro-metastases it is not possible to propose to avoid cALND. When SN was involved by ITC or micro-metastases, omission of cALND is still controversial and should have a negative prognosis impact in relation with a down staging and under treatment.

Background

A decrease of axillary lymph node dissection (ALND) rate since the development and
validation of sentinel lymph node biopsy (SLNB) for non-involved sentinel node (SN)\(^1\) has been observed. More recently, since results of ACOSOG Z0011, IBCSG 23-01 and AATRM trials\(^2, 3, 4\), complementary ALND (cALND) was questioned in some situations for involved-SN. However, few studies were reported about SLNB accuracy for patients who need total mastectomy.

In Z0011 trial\(^2\) patients undergoing upfront conservative surgery followed by systemic adjuvant therapy for unifocal breast cancer (BC) with 1 or 2 SN involved by micro or macro-metastases, without capsular rupture, were included. Results were discussed concerning the limits and the biases of this study\(^5, 6\). Omission of cALND was held in some teams and recommendations\(^7, 8\), underlining the strict conditions of possible omission of cALND. An evaluation in selected patients considered at high-risk was reported\(^9\). But some points remains unclear, particularly for patients who required total mastectomy. The possibility of cALND avoidance for patients who required total mastectomy is a timely topic. Very few patients with mastectomy were included in randomized trial\(^3, 4\) and only for patients with pN0(i+) or pN1mi SN (86 patients in IBCSG 23-01 trial and 18 in AATRM trial). For this reason we designed the SERC trial to compare outcomes in patients with SN-involvement treated with cALND or no further treatment to the axilla with larger inclusion criteria\(^10, 11\).

The aim of this study was to examine involved non-sentinel node (NSN) rate, axillary recurrence (AR) rate and mainly survival according to SN status among a multi-institutional cohort of patients who required total mastectomy.

Methods

We conducted a retrospective analysis of 2423 consecutive patients managed between
March 1999 and December 2012 in 9 specialized breast centers, referred for mastectomy and SLNB (not included in SERC trial) among a breast cancer data base of 23145 patients. Total mastectomy was usually proposed to manage multi focal tumors, small invasive BC with a large in situ component, patients with a very small breast volume and patient’s choice for total mastectomy.

All patients included in this study have been managed for early BC <= cT2-N0, without pre-operative treatment before SLNB and total mastectomy. We excluded patients with axillary cN1 or T3-4. SLNB was performed using combined isotopic and colorimetric detection or isotopic detection alone with peri-tumoral and/or sub areolar injection\textsuperscript{11}.

Although the methods used for SN histological examination were not standardized in the protocol, all sites proceeded similarly: serial sections were performed every 200 microns and stained with standard HE. The number of sections was six to ten, or pursued until node exhaustion in case of large SN. Additional IHC analysis was done in case of negative results at standard examination. For lymph nodes (LN) identified by cALND, routine HE analysis was performed\textsuperscript{10,11}.

For data analysis, we used:

Five tumor subtypes were defined according to immunohistochemistry (IHC) analysis of endocrine receptors (ER) and Her2: Luminal-A (ER+ Her2- Grade 1-2, Her2 (Her2+ ER-), Triple negative (ER- Her2--: negative estrogen and progesterone receptors), Luminal-B Her2- Grade 3, Luminal-B Her2+ ER+ \textsuperscript{8,9}. ERs (Estrogen receptor and/or progesterone receptor expression) were considered as positive if they were expressed in at least 10% of the tumor specimen. HER2 status was determined according to French guidelines by IHC +/- fluorescent in situ hybridization.

Statistical analysis: Four categories of SN-status were defined: negative-SN (pN0i-),
isolated tumor cells (ITC: pN0(i+)$ \leq 0.2$mm), detected either by hematoxylin and eosin (HE) staining or by cytokeratin IHC, micro-metastases (pN1mi $>0.2$mm and $\leq 2$mm), and macro-metastases ($>2$mm)$^{10-12}$.

We have analyzed involved non-sentinel node (NSN) rate at cALND and predictive factors of NSN involvement. Then we have evaluated axillary recurrence (AR) rate, overall survival (OS) and disease-free survival (DFS) according to cALND or not. We used standard descriptive statistics (mean, standard deviation [SD], median and range for quantitative variables, count and frequency for categorical variables) to describe patients and tumors characteristics. In univariate analyses, comparisons were performed using Chi Square. Multivariable analysis was performed using binary logistic regression. Survival analysis was performed using Log Rank test for univariate analysis and Cox model for multivariate analysis. Overall survival was defined as the time elapsed between surgery and death from any cause. Disease-free survival was calculated from the date of surgery to the first date of loco-regional recurrence, distant recurrence or death from any cause, whichever occurred first.

All statistical analyses were conducted using SPSS 16.0. All statistical tests were two-sided. The level of statistical significance was set at a p value of 0.05.

All procedures performed in this study involving human participants were done in accordance with the French ethical standards and with the 2008 Helsinki declaration. This work was approved by our institutional review board (IPC Comité d'Oriention Stratégique).

Results

Population

Among 2423 patients with SLNB for BC mastectomy we reported 1307 pN0(i-)SN, 120
pN0(i+)SN, 273 pN1miSN and 723 pN1macroSN. cALND has been performed for 1306 patients (53.9%), in 24.5, 73.3, 82.4 and 93.1% for SN pN0(i-), pN0(i+), pN1mi and pN1macro, respectively. Factors associated with pN final status with or without cALND are reported in Table 1.

Median follow-up was 42.72 months (mean: 51.33, CI95%: 49.9-52.8, range: 0.26-211). We reported 120 death and 213 recurrences including 152 metastases and 21 axillary recurrences and 40 local breast recurrence or unknown as first event.

**pN0(i-) SN status**

Among 1307 patients with pN0(i-)SN, 320 underwent an additional ALND, mainly before publication of NSABP B-32 trial results. We observed 35 LN macro metastases at cALND (10.9%) and false negative rate (FNR) was 3.63% among 964 patients with LN involvement (35/964) at cALND with pathologic results known or at SN.

In binary logistic regression, cALND was significantly associated with grade, LVI, ER, tumor size and periods of treatment. Adjuvant chemotherapy (AC), post-mastectomy radiotherapy (PMRT) and regional nodal irradiation (RNI) were delivered more frequently for patients with cALND, including 95.4% (21/22) of AC and 97.1% (34/35) of PMRT for patients with involved NSN at cALND. (Table 2).

In Cox regression analysis, OS and DFS were not significantly different according to cALND or not (Table 3, 4). AR rates were 1.4% for patients without cALND (14/987) and 0.3% with cALND (1/320) (p: 0.086): 2.8% (9/323) and 0.8% (5/660) for patients without cALND respectively with and without PMRT, 0.4% (1/225) and 0% (0/95) for patients with cALND respectively with and without PMRT (p: 0.039: cALND or not for patients with PMRT).

**pN1 macro metastases SN status**

Among 723 patients with SN macro-metastases, cALND was omitted in only 50 patients (6.9%). Among patients with involved-SN number known, only one SN macro-metastases...
was observed in 372 patients and more than one in 257 patients: 124 patients with only one SN macro-metastases had one or more NSN-involved at cALND (124/332: 37.3%). AC and PMRT were delivered more frequently for patients with cALND (Table 2). In Cox regression analysis, OS and DFS were not significantly different according to cALND or not (Table 3, 4). AR rates were 1.0 and 0% respectively for patients with and without cALND (7/673 vs 0/50), 0.9% and 2.5% respectively for patients with and without PMRT (6/683 vs 1/40: p=0.330).

**pN0(i+) and pN1mi SN status**

Among 120 patients with pN0(i+) SN and 273 patients with pN1mi SN, cALND were respectively omitted in 32 patients (26.7%) and 48 patients (17.6%) (Table 2). One or several macro-metastases in NSN at cALND was observed in 6 patients with pN0(i+) SN (6/88: 6.8%, 1 NSN positive for 4 patients, 2 and 6 NSN positive for 2 others) and 30 patients with pN1mi (30/225: 13.3%, 1 NSN positive for 21 patients, 2 NSN positive for 7 patients, 3 and 6 NSN positive for 2 others).

In univariate analysis, age, pT size and SN status were significantly predictive of NSN involvement among patients with pN0(i+) or pN1mi SN and cALND (Table 5). These factors remained significant in binary logistic regression (Table 5).

Four groups were determined according to pT tumor size < or >= 20mm and age > or <= 40 years-old with NSN involvement rate for pN0(i+) and pN1mi from 0 to 65%. In binary logistic regression cALND was not significantly associated to these 4 sub-groups and SN status (Table 6).

For pN0(i+) and for pN1mi, AC and PMRT was delivered more frequently for patients with cALND, including for patients with involved NSN at cALND 100% (5/5) and 92.3% (24/26) of AC, 83.3% (5/6) and 100% (30/30) of PMRT for pN0(i+) and pN1mi respectively (Table 2). For pN0(i+) and pN1mi according to cALND or not, PMRT rate was significantly different
only for patients with pT<20mm/age>40 years-old, RNI rate was significantly different for patients with pT<20mm/age>40 years-old and pT<20mm/age<=40 years-old, AC rate was significantly different for patients with pT<20mm/age>40 years-old and pT>=20mm/age>40 years-old (Supplementary Table 1).

In binary logistic regression, PMRT, RNI and AC were significantly associated with cALND but also to SN status and pT/age sub-groups (Table 6).

In univariate analysis (Log Rank), OS and DFS was lesser and significantly different for patients with pN0(i+) SN without cALND (respectively, p: 0.012 and <0.0001), but without difference for pN1mi SN (respectively, p: 0.985 and 0.180). In Cox regression analysis (Tables 3-4), OS were not significantly different according to cALND or not for patients with pN0(i+) or pN1mi (HR: 2.063, CI95%: 0.439-9.693, p: 0.359) and a significant difference was observed for DFS with lesser survival rate for patients without cALND (HR: 3.861, CI95%: 1.660-8.982, p: 0.002) without other significant criteria (ET, AC, LVI, age, SN status, PMRT and RNI) (Fig. 1).

In Cox regression analysis adjusted on endocrine therapy (ET), SN status and pT/age (< or >=20mm/<= or >40 years-old), omission of cALND was negatively associated to DFS (HR: 4.023, CI95%: 1.896-8.534, p<0.001) and no ET had also a borderline negative association (HR: 2.755, CI95%: 0.988-7.684, p: 0.053). Omission of cALND and no ET were negatively associated to RFS (respectively, HR: 3.187, CI95%: 1.379-7.363, p: 0.007 and HR: 3.968, CI95%: 1.399-11.25, p: 0.010). On OS adjusted on ET, SN status, pT/age (< or >=20mm/<= or >40 years-old), LVI, only no ET was negatively associated to OS (HR: 7.985, CI95%: 1.346-47.37, p: 0.022) without significant difference for cALND or not (HR: 2.904, CI95%: 0.733-11.51, p: 0.129).

AR rates were no significantly different according to cALND or not and PMRT or not, 0% (0/31) and 0% (0/49) for patients without cALND, 0.8% (2/246) and 1.5% (1/67) for
patients with cALND respectively with and without PMRT.

Conclusions

We reported from a large retrospective cohort of mastectomy, no OS and DFS significant difference between cALND or not for patients with pN0(i-) SN status and for patients with pN1 macro metastases SN status. However, few patients with pN1 macro metastases SN had no cALND. For patients with pN0(i+) or pN1mi SN, lesser DFS was reported for patients without cALND in comparison with patients with cALND in multivariable analysis (HR: 3.861, p: 0.002) bur without significant difference for OS.

For patients with pN0(i-) SN, we reported analysis of 1307 patients without cALND in 75.5% of patients. In Veronesi et al trial\textsuperscript{13}, randomization of cALND was proposed for patients cN0 with tumor diameter of 2cm or less and breast conserving surgery: 8 positive NSN at cALND were reported (8/257: 3.1%) with 8.8% FNR (8/91). In NSABP-B32 trial\textsuperscript{1}, randomization of cALND was proposed for patients cN0 with unifocal tumor, mainly <=20mm (83.8%: 3344/3989) with conservative treatment (87.5%) or mastectomy (n=499, 12.5%). In cALND arm, 75 patients (75/1975: 3.8%) had positive NSN with a FNR > 8.3% (75 among 904 patients with SN positive or unknown). FNR was lower in our study (3.63%). A lower rate of FNR should be attributed to more extensive SN pathologic analysis in our study with serial sections and IHC for negative HE analysis. After more extensive pathologic analysis, it was reported that 15.9% (CI95%: 14.7-17.1%) of SN (616/3884) presented occult metastases (69.8% among ITC: 430/616 and 27.9% among micro-metastases: 172/616) and in some cases macro-metastases (2.3% of macro-metastases: 14/616)\textsuperscript{14}. It had been reported that SLNB was accurate for large tumors (1101 with tumors > 20 and <30mm and 748 tumors >=30mm)\textsuperscript{15} and for multi-focal multicentric tumors\textsuperscript{16} even if LN involvement rate was higher for these patients.
For patients who had a macro-metastases SN, the only reported trial with cALND randomization versus only SLNB\(^2\) had included macro and micro-metastases only for conservative treatment. In AMAROS trial\(^ {17}\), with randomization between cALND versus axillary radiotherapy, patients with tumors up to 5cm diameter, cN0, unifocal or multifocal and breast-conserving treatment or mastectomy were eligible: 19.4% of patients had tumors more than 2cm (276/1425), 17.4% had mastectomy (248/1425), 60.4% had macro-metastases SN (861/1425), 28.8% had micro-metastases SN (410/1425) and 10.8% had ITC SN (154/1425). In the cALND arm, involved NSN rate was 32.8% (220/671). In NSABP B-04 trial with randomization between ALND or no axillary surgery for patients with total mastectomy, no survival impact was observed with a long follow-up\(^ {18}\). However, patients included in this trial had large tumors, which were very different with patients for whom SLNB is indicated, and any systemic treatment was administered with low survival rates in two arms. Omission of regional treatment with ALND had in consequence no survival impact.

In OTOASOR trial\(^ {19}\), with randomization between cALND versus axillary radiotherapy, patients with tumors up to 3cm diameter, cN0, unifocal or multifocal and breast-conserving treatment or mastectomy were eligible: 48.7% of patients had tumors more than 2cm (231/474) with 11.1% of multifocal tumors (53/474), 15.6% had mastectomy (74/474), 60.4% had macro-metastases SN (139/230), 33.5% had micro-metastases SN (77/230) and 6.1% had ITC SN (14/230) in the radiotherapy arm. In the cALND arm, involved NSN rate was 38.5% (94/244).

Several trials are ongoing with randomization of cALND: INSEMA trial with only 1 or 2 SN macro-metastases and conservative treatment\(^ {20}\), POSNOC trial with only 1 or 2 SN macro-metastases and conservative treatment or mastectomy with cALND or radiotherapy versus
no other axillary treatment\textsuperscript{21}, SERC trial\textsuperscript{10, 11} and BOOG 2013–07 trial for mastectomy and 1 to 3 involved SN by micro or macro-metastases with only mastectomies\textsuperscript{22}, SENOMAC trial for patients with 1 or 2 SN macro-metastases including mastectomies\textsuperscript{23}.

In SERC trial\textsuperscript{10, 11}, 1897 patients are actually included with randomization between cALND or no other treatment for involved SN by ITC or micro-metastases or macro-metastases with conservative treatment or mastectomy. In the first 963 patients included in the first analysis (170 mastectomies and 793 conservative treatment), the overall rate of positive NSN was 19\% (84/442) for patients with cALND, and crude rates of positive NSN according to SN status were 4.5\% for patients with ITC (1/22), 9.5\% for SN micro-metastases (13/137), 23.9\% for SN macro-metastases (61/255).

For patients with pN0(i+) or pN1mi SN, two trials were reported with randomization of cALND\textsuperscript{3, 4} with 86 mastectomies in IBCSG 23-01 trial (86/931: 9.2\%) and the rate of involved NSN in cALND arm was 13\%. In AATRM trial only 18 patients had had mastectomy\textsuperscript{4}. In the study published by Tvedskov et al., these rates of involved NSN were 9.2\% for ITC and 17.9\% for Mic\textsuperscript{24} and in a previous study we had reported positive-NSN rates of 13.9\% (40/287) for ITC and 14.1\% (93/658) for pN1mi SN with a predictive nomogram based on tumor size, ratio of positive-SN/analyzed-SN, LVI, tumor histologic type\textsuperscript{15, 25}.

AC rate was not higher for patients without cALND for pN0(i+) and pN1mi in comparison with patients with ALND in our study, respectively 59.4\% and 39.6\% versus 34.1\% and 21.3\%.

In the AMAROS trial\textsuperscript{17}, ALND realization had no impact on the decision of adjuvant treatment. In a study in 172 patients with pN1mi SN who underwent cALND, Mazouni et
al.\textsuperscript{26} showed the low impact of SN status in the therapeutic decision for AC, except in case of low grade or HER2-negative tumors. However, in the study by Aigner et al.\textsuperscript{27}, indication of AC was modified in 18.2\% of cases. In the Multicenter Clinical Trial AATRM\textsuperscript{4}, 247 patients with Mic were randomized between cALND and no cALND and AC rate was higher in those who underwent cALND (40.2\%) compared to those without cALND (36.8\%). Finally, in the study by Savolt et al. with randomization between cALND and regional node RT, AC was more frequently administered in case of cALND (78 versus 69\%)\textsuperscript{19}. In IBCSG trial AC was not different between cALND and no cALND: 32.1\% (149/464) and 29.1\% (136/467)\textsuperscript{3}. Indications of AC depended of tumor phenotype and molecular tumor subtypes but also of presence or no of axillary lymph node macro-metastases. Under evaluation of axillary LN status with omission of cALND could resulted in AC under indication, particularly for Luminal-A or Luminal-B Her2-negative tumors.

PMRT rate was not lower in our study for pN0(i+) and pN1mi for patients with cALND versus cALND (respectively, 34.1\% and 21.3\% versus 59.4\% and 39.6\%). In IBCSG 23-01 trial, no PMRT was realized in all patients with mastectomy. The role of RT in the absence of cALND in patients with invaded SN has been extensively discussed\textsuperscript{28}. In the ACOSOG Z0011 trial, adjuvant treatments associated with whole breast irradiation (WBI) using axillary tangential fields, likely contributed to the low rate of node recurrence (1\% in the group without ALND). However, WBI with tangential fields and regional RT were specified in only one third of cases\textsuperscript{29}. Most series evaluating the SN technique showed that tangential fields include the majority of levels I and II but others reported that standard tangential fields of breast RT include the axillary only to a limited extent\textsuperscript{30, 31}. AR is a rare event corresponding to a strong survival pejorative factor\textsuperscript{32}. 
In Gentilini et al. study, AR rates were significantly different between patients who received WBI or partial breast irradiation after conservative treatment\textsuperscript{33}. At 10-years, AR rate were in IBCSG 23-01 trial 1.2% and 1.2% for 86 mastectomies respectively in arm with ALND (1/44) and without cALND (1/42) but AR rates for patients with conservative treatment with IORT without WBI were 0% (0/79) in arm with cALND and 6.25% (5/80) in arm without cALND. In our study, AR rates were no significantly different according to cALND or not and PMRT or notPMRT is usually indicated for patients with lymph node macro-metastases\textsuperscript{34}. Two trials explored omission of cALND for patients with positive-SN treated by mastectomy with determination of tangential fields: BOOG 2013–07 and SERC trials\textsuperscript{10, 11, 22}.

Abbreviations

AC : Adjuvant chemotherapy
ALND : axillary lymph node dissection
AR : axillary recurrence
BC : breast cancer
cALND : complementary axillary lymph node dissection
DFS : disease-free survival
ER : endocrine receptors
ET : endocrine therapy
FNR : false negative rate
HE : hematoxylin and eosin
HR : hazard ratio
IHC : immunohistochemistry
IORT : intra operative radiotherapy
ITC : isolated tumor cells
LN : lymph nodes
LVI : lympho vascular invasion
NSN : non-sentinel node
OS : overall survival
PMRT : post-mastectomy radiotherapy
RNI : regional nodal irradiation
RT : radiotherapy
SD : standard deviation
SLNB : sentinel lymph node biopsy
SN : sentinel node
WBI : whole breast irradiation

Declarations

Ethics approval and consent to participate :
This work was approved by our institutional review board (IPC - Comité d'Orienta
tion Stratégique).
All procedures performed in this study involving human participants were done in
accordance with the French ethical standards and with the 2008 Helsinki declaration.
All included patients provided written informed consent before surgery, including the use
of their data for research.

Availability of data and material :
Administrative data and clinical data are compiled in a common database and are
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Authors' contributions:

GH, JMC, GB, CM, FR, PG, ED, ASA, PEC, MB, EL, MC supervised or participated in the data collection.

GH and MC conducted data analyses and interpreted the results.

GH and MC drafted the manuscript.

GH, JMC, GB, CM, FR, PG, ED, ASA, PEC, MB, EL, MC participated in revisions of the manuscript.

GH, JMC, GB, CM, FR, PG, ED, ASA, PEC, MB, EL, MC have read and approved the final manuscript.

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Tables

**Table 1:** Characteristics of patients according to pN status.

| pN final status | pN0 | pN0(i+) | pN1mi | pN1 macro | T |
|----------------|-----|---------|-------|-----------|---|
|                | Nb  | %       | Nb    | %         | Nb | %    | Nb   | %    | Nb   |
| Total          | 1272| 52.5    | 11    | 4.7       | 243| 10.0  | 794  | 32.8  | 2423 |
| SN alone       |     |         |       |           |    |       |      |       |      |
| pN0(i-) sn     | 987 | 88.4    | 32    | 2.9       | 48 | 4.3   | 50   | 4.5   | 1117 |
| pN0(i+) sn     | 285 | 89.1    | 0     | 0         | 0  | 35    | 10.9 | 320   |
| pN1 mi sn      | 0   | 82      | 93.2  | 0         | 6  | 6.8   | 88   |       |      |
| pN1 macro sn   | 0   | 0       | 195   | 86.7      | 30 | 13.3  | 225  |       |      |

21
| age     |   |   |   |   |   |   |
|---------|---|---|---|---|---|---|
|         | ≤40| 7.9| 23| 20.| 32| 13.|
| 40.1-50 | 317| 24.9| 29| 25.| 460| 24.|
| 50.1-74.9 | 718| 56.4| 56| 49.| 125| 51.|
| ≥ 75    | 136| 10.7| 6 | 5.3| 26 | 10.|
|         |   |   |   |   |   |   |
| pT mm   |   |   |   |   |   |   |
| 0-5     | 176| 14.3| 9 | 8.0| 18 | 7.5|
| >5-10   | 260| 21.2| 19| 17.| 30 | 12.|
| >10-20  | 387| 31.5| 27| 24.| 79 | 32.|
| 21-50   | 344| 28.0| 43| 38.| 80 | 33.|
| >50     | 61 | 5.0 | 14| 12.| 34 | 14.|
| Grade   |   |   |   |   |   |   |
| 1       | 351| 27.6| 20| 17.| 70 | 28.|
| 2       | 618| 48.6| 65| 57.| 116| 47.| 70 | 427| 53.|
| 3       | 246| 19.3| 24| 21.| 51 | 21.|
| unknown | 57 | 4.5 | 5 | 4.4| 6  | 2.4|
| LVI     |   |   |   |   |   |   |
| No      | 950| 86.8| 69| 63.| 135| 63.|
| Yes     | 144| 13.2| 39| 36.| 77 | 36.|
| unknown | 327|   |   |   |   |   |
| ER      |   |   |   |   |   |   |
| positive| 1072| 84.3| 10| 89.| 225| 92.|
| negative| 171| 13.4| 9 | 7.9| 16 | 6.5|
| unknown | 29 | 2.3 | 3 | 2.6| 2  | 0.8|
| Her2    |   |   |   |   |   |   |
| positive| 160| 13.7| 17| 17.| 26 | 12.|
| negative| 955| 81.8| 71| 73.| 171| 83.|
| unknown | 52 | 4.5 | 9 | 9.3| 7  | 3.4|
| Histology |   |   |   |   |   |   |
| Ductal  | 925| 72.7| 76| 66.| 176| 72.|
| Lobular | 225| 17.7| 26| 22.| 38 | 15.|
| Mixt    | 26 | 2.0 | 6 | 5.3| 7  | 2.9|
| Others  | 96 | 7.5 | 6 | 5.3| 22 | 9.1|
| T subtypes |   |   |   |   |   |   |
| Lum A   | 775| 69.8| 54| 61.| 134| 68.|
| Lum B HER- | 96| 8.6 | 15| 17.| 31 | 15.|
| Lum B HER+ | 90| 8.1 | 10| 11.| 18 | 9.1| 69 | 9.7| 187|
Abbreviation: SN: sentinel node; ALND: axillary lymph node dissection; ER: endocrine receptor; LVI: lympho vascular invasion; PMRT: post-mastectomy radiotherapy; RNI: regional nodal irradiation;

Table 2: Characteristics of patients according to sentinel node status and cALND or not.

| HER2 | 70 | 6.3 | 7 | 8.0 | 8 | 4.1 | 61 | 8.6 | 146 |
|------|----|-----|---|-----|---|-----|----|-----|-----|
| TN   | 80 | 7.2 | 2 | 2.3 | 6 | 3.0 | 46 | 6.5 | 134 |

Chemotherapy

|                   | No       | 762 | 59.9 | 49 | 43.0 | 65 | 26.7 | 64 | 8.1 | 940 |
|-------------------|----------|-----|------|----|------|----|------|----|-----|-----|
|                   | Yes adjuvant | 493 | 38.8 | 63 | 55.3 | 167 | 68.7 | 663 | 83.5 | 1386 |
|                   | Yes Neo adjuvant | 12 | 0.9 | 2 | 1.8 | 10 | 4.1 | 66 | 8.3 | 90  |
| unknown           | 5 | 0.4 | 0 | 1 | 0.4 | 1 | 0.1 | 7  |      |     |

Endocrine Therapy

|                   | No       | 281 | 22.2 | 18 | 15.8 | 26 | 10.8 | 135 | 17.1 | 460 |
|-------------------|----------|-----|------|----|------|----|------|----|------|-----|
|                   | Yes      | 985 | 77.8 | 95 | 84.2 | 214 | 89.2 | 654 | 82.9 | 1949 |
| unknown           |          |     |      |    |      |    |      |    |      | 14  |

Trastuzumab

|                   | No       | 1048 | 90.1 | 10 | 88.6 | 219 | 90.1 | 680 | 86.6 | 2048 |
|-------------------|----------|------|------|----|------|----|------|----|------|-----|
|                   | Yes      | 115  | 9.9  | 13 | 11.4 | 24  | 9.9  | 105 | 13.4 | 257  |
| unknown           |          |      |      |    |      |    |      |    |      | 1    |

PMRT

|                   | No       | 754  | 59.4 | 39 | 34.2 | 58  | 23.9 | 42  | 5.3  | 893 |
|-------------------|----------|------|------|----|------|----|------|----|------|-----|
|                   | Yes      | 514  | 40.5 | 75 | 65.8 | 185 | 76.1 | 752 | 94.7 | 1526 |
| unknown           |          | 1    | 0.1  | 0  | 0    | 0   | 0    | 0   | 1    |     |

RNI

|                   | No       | 1000 | 84.8 | 57 | 58.8 | 104 | 48.8 | 77  | 11.2 | 1238 |
|-------------------|----------|------|------|----|------|----|------|----|------|-----|
|                   | Yes      | 179  | 15.2 | 40 | 4.3  | 109 | 51.2 | 611 | 88.8 | 939  |
| unknown           |          | 246  |      |    |      |    |      |    |      |      |

| SN status | pN0 | pN0(i+) | SN+ALND | SN | Chi2 | SN+ALND | SN | Chi2 |
|-----------|-----|---------|---------|----|------|---------|----|------|
| pN final  |     |         |         |    |      |         |    |      |
| pN0       | 285 | 987     |         |    |      |         |    |      |
| pN0(i+)   |     | 82      | 32      |    |      |         |    |      |
| pN1mi     | 35  | 0       | 6       |    | 0    |         |    |      |
| pN1macro  |     |         |         |    |      |         |    |      |
| age       |     |         |         |    |      |         |    |      |
| <= 40     | 20  | 82      | 0.218   |    | 16   | 8       |    | 0.54 |
| 40.1-50   | 89  | 239     | 22      |    | 8    | 8       |    |      |
| Grade          | Overall Survival | ER+  | ER-  | ER+  | ER-  |
|----------------|------------------|------|------|------|------|
| 1              | 185              | 66   | 287  | 18   | 3    |
| 2              | 179              | 179  | 460  | 47   | 22   |
| 3              | 69               | 69   | 189  | 20   | 5    |
| unknown        | 6                | 6    | 18   | 3    | 2    |
| LVI No         | 185              | 66   | 287  | 18   | 3    |
| LVI Yes        | 55               | 179  | 460  | 47   | 22   |
| Endocrine Yes  | 56               | 69   | 189  | 20   | 5    |
| Endocrine No   | 262              | 262  | 750  | 76   | 26   |
| Chemotherapy No| 140              | 215  | 676  | 53   | 21   |
| Chemotherapy Yes| 160           | 20   | 63   | 2    | 0    |
| Chemotherapy Neo| 19            | 16   | 57   | 5    | 2    |
| Chemotherapy unknown| 1      | 21   | 75   | 6    | 4    |
| PMRT No        | 95               | 140  | 623  | 30   | 19   |
| PMRT Yes       | 225              | 225  | 354  | 55   | 13   |
| RNI No         | 211              | 211  | 794  | 41   | 18   |
| RNI Yes        | 101              | 101  | 107  | 35   | 8    |

**Table 3:** Overall Survival according to sentinel node status: multivariable analysis.
| Overall Survival | pN0 SN | pN0(i+) & pN1mi SN | pN1 macro SN |
|------------------|--------|---------------------|--------------|
|                  | HR | CI95% | p  | HR | CI95% | p  | HR |
| ALND             |    |       |    |    |       |    |    |
| Yes              | 1  |       |    |    |       |    |    |
| No               | 1.472 | 0.614-3.526 | 0.386 | 2.063 | 0.439-9.693 | 0.359 |
| Grade            |    |       |    |    |       |    |    |
| 1                | 1  |       |    |    |       |    |    |
| 2                | 0.551 | 0.225-1.350 | 0.192 |    |       |    |    |
| 3                | 1.238 | 0.501-3.057 | 0.644 |    |       |    |    |
| LVI              |    |       |    |    |       |    |    |
| No               | 1  |       |    |    |       |    |    |
| Yes              | 2.293 | 1.010-5.205 | 0.047 | 0.775 | 0.181-3.314 | 0.731 |
| Endocrine therapy|    |       |    |    |       |    |    |
| Yes              | 1  |       |    |    |       |    |    |
| No               | 3.044 | 1.484-6.247 | 0.002 | 6.924 | 1.087-44.09 | 0.040 |
| age              |    |       |    |    |       |    |    |
| <= 40           | 1  |       |    |    |       |    |    |
| 40.1-50         | 0.280 | 0.069-1.140 | 0.076 | 0.628 | 0.037-10.58 | 0.747 |
| 50.1-74.9       | 0.610 | 0.205-1.813 | 0.374 | 1.521 | 0.164-14.14 | 0.712 |
| >= 75           | 2.499 | 0.730-8.558 | 0.145 | 1.957 | 0.136-28.14 | 0.622 |
| pN final        |    |       |    |    |       |    |    |
| pN0              | 1  |       |    |    |       |    |    |
| pN1macro         | 7.180 | 2.031-25.38 | 0.002 |    |       |    |    |
| Chemotherapy     |    |       |    |    |       |    |    |
| No               | 1  |       |    |    |       |    |    |
| Yes              | 0.347 | 0.074-1.619 | 0.178 |    |       |    |    |
| NAC              |    |       |    |    |       |    |    |
| PMRT             |    |       |    |    |       |    |    |
| No               | 1  |       |    |    |       |    |    |
| Yes              | 0.289 | 0.024-3.486 | 0.328 |    |       |    |    |
| RNI              |    |       |    |    |       |    |    |
| No               | 1  |       |    |    |       |    |    |
| Yes              | 5.095 | 0.350-74.16 | 0.233 |    |       |    |    |

Legend: Significant univariate variables were included in each model.

Abbreviations: HR: hazard ratio; ALND: axillary lymph node dissection; LVI: lymph vascular invasion; PMRT: post-mastectomy radiotherapy; RNI: regional nodal irradiation;

Table 4: Disease Free Survival according to sentinel node status: multivariable analysis.
| Grade     | 1     | 1          |     |     |     |     |
|-----------|-------|------------|-----|-----|-----|-----|
| 2         | 0.883 | 0.453-1.722| 0.715|     |     |     |
| 3         | 1.893 | 0.858-4.178| 0.114|     |     |     |
| LVI       |       |            |     |     |     |     |
| No        | 1     | 1          |     |     |     |     |
| Yes       | 2.031 | 1.050-3.928| **0.035** | 1.136 | 0.508-2.542 | 0.756 |
| Endocrine therapy |       |            |     |     |     |     |
| Yes       | 1     | 1          | 1   |     |     |     |
| No        | 3.190 | 1.785-5.703| **<0.0001** | 2.450 | 0.770-7.799 | 0.129 | 2.52 |
| SN status |       |            |     |     |     |     |
| pN0(i-)   |       |            |     |     |     |     |
| pN0(i+)   |       |            |     |     |     |     |
| pN1mi     |       | 0.708      | 0.315-1.592| 0.404 |     |     |
| pN1macro  |       |            |     |     |     |     |
| T size    |       |            |     |     |     |     |
| <=5mm     | 1     |            |     |     |     |     |
| 5.1-10    | 3.016 | 0.826-11.01| 0.095|     |     |     |
| 10.1-19.9 | 4.087 | 1.153-14.48| **0.029** |     |     |     |
| 20-50     | 4.874 | 1.356-17.52| **0.015** |     |     |     |
| >50mm     | 6.537 | 1.583-26.99| **0.009** |     |     |     |
| age       |       |            |     |     |     |     |
| <= 40     | 1     |            |     |     |     |     |
| 40.1-50   | 0.886 | 0.276-2.846| 0.839 | 0.773 | 0.245-2.442 | 0.661 | 0.79 |
| 50.1-74.9 | 0.967 | 0.335-2.791| 0.950 | 0.689 | 0.240-1.976 | 0.489 | 1.07 |
| >= 75     | 1.821 | 0.532-6.233| 0.340 | 0.578 | 0.125-2.686 | 0.485 | 1.52 |
| Chemotherapy |       |            |     |     |     |     |
| No        | 1     |            |     |     |     |     |
| Yes       | 0.446 | 0.221-0.901| **0.024** | 1.164 | 0.413-3.280 | 0.774 | 0.96 |
| NAC       | 0.000 | 0.0-8.4E256| 0.971 | 2.841 | 0.280-28.87 | 0.377 | 1.44 |
| PMRT      |       |            |     |     |     |     |
| No        | 1     |            |     |     |     |     |
| Yes       | 0.472 | 0.145-1.538|     | 0.213 |     | 2.12 |
| RNI       |       |            |     |     |     |     |
| No        | 1     |            |     |     |     |     |
| Yes       | 1.015 | 0.345-2.985| 0.978 |     |     |     |

Legend: Significant univariate variables were included in each model.

DFS: Disease Free Survival; HR: hazard ratio
SN: sentinel node; ALND: axillary node dissection; LVI: lympho vascular invasion; PMRT: post-mastectomy radiotherapy; RNI: regional nodal irradiation.
Table 5: Binary logistic regression predictive of positive NSN.

|                  | pN0(i+) & pN1mi with ALND |                  |                  |
|------------------|-----------------------------|------------------|------------------|
|                  | univariate                  | Regression       |
|                  | p   | OR   | CI95%  | p     |
| age              |     |      |        |       |
| > 40             | 0.013 | 1 |       |       |
| <= 40            | 2.306 | 1.078-4.932 | 0.031 | |
| pT size          |     |      |        |       |
| < 20mm           | 0.003 | 1 |       |       |
| >= 20mm          | 2.603 | 1.426-4.751 | 0.002 | |
| SN status        |     |      |        |       |
| pN0(i+)          | <0.0001 | 1 |       |       |
| pN1mi            | 4.825 | 1.930-12.06 | 0.001 | |
| Grade            |     |      |        |       |
| 1 vs 2 vs 3      | 0.617 |      |       |       |
| LVI              |     |      |        |       |
| No vs Yes        | 0.430 |      |       |       |
| ER               |     |      |        |       |
| No vs Yes        | 0.340 |      |       |       |
| Periods          |     |      |        |       |
| P1 vs P2 vs P3   | 0.170 |      |       |       |
| Her2/ER          |     |      |        |       |
| ER+ Her2-        | 0.255 |      |       |       |

Abréviation: ALND : axillary lymph node dissection; SN : sentinel node; LVI : lympho vascular invasion ; ER : endocrine receptor;

Table 6: PMRT, RNI and AC realization: binary logistic regression.

|                  | PMRT |                  | RNI  |                  |
|------------------|------|------------------|------|------------------|
|                  | OR   | CI95%  | p | OR   | CI95%  | p     |
| cALND or no      | SN+cALND | 1 |       | 1 |       |       |       |
|                  | SN   | 0.477 | 0.273-0.833 | 0.009 | SN   | 0.436 | 0.244-0.779 | 0.005 |
|                  | pN0(i+) | 1 |       | 1 |       |       |       |
|                  | pN1mi | 1.905 | 1.134-3.201 | 0.015 | pN1mi | 1.629 | 0.991-2.678 | 0.055 |
|                  | > 40 years | pT < 20mm | 1 |       | 1 |       |       |       |
|                  |      | 3.019 | 1.774-5.137 | <0.0001 | 2.155 | 1.322-3.513 | 0.002 |
|                  | <= 40 years | pT < 20mm | 2.168 | 0.885-5.312 | 0.090 | 1.222 | 0.541-2.761 | 0.630 |
|                  |      | 17.82 | 2.330-136.3 | 0.006 | 4.545 | 1.692-12.21 | 0.003 |

évictions: PMRT : post-mastectomy radiotherapy ; RNI : regional nodal irradiation ; AC : adjuvant chemotherapy; cALND : complementary axillary lymph node dissection ; SN : sentinel node;

Figures
Figure 1

DFS for pN0(i+) and pN1mi according to cALND or not, adjusted in multivariable analysis.

Supplementary Files

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