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CLINICAL TRIAL

Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study

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Abstract

Purpose GANEA2 study was designed to assess accuracy and safety of sentinel lymph node (SLN) after neo-adjuvant chemotherapy (NAC) in breast cancer patients.

Methods Early breast cancer patients treated with NAC were included. Before NAC, patients with cytologically proven node involvement were allocated into the pN1 group, other patient were allocated into the cN0 group. After NAC, pN1 group patients underwent SLN and axillary lymph node dissection (ALND); cN0 group patients underwent SLN and ALND only in case of mapping failure or SLN involvement. The main endpoint was SLN false negative rate (FNR). Secondary endpoints were predictive factors for remaining positive ALND and survival of patients treated with SLN alone.

Results From 2010 to 2014, 957 patients were included. Among the 419 patients from the cN0 group treated with SLN alone, one axillary relapse occurred during the follow-up. Among pN1 group patients, with successful mapping, 103 had a negative SLN. The FNR was 11.9% (95% CI 7.3–17.9%). Multivariate analysis showed that residual breast tumor size after NAC ≥ 5 mm and lympho-vascular invasion remained independent predictors for involved ALND. For patients with initially involved node, with negative SLN after NAC, no lympho-vascular invasion and a remaining breast tumor size 5 mm, the risk of a positive ALND is 3.7% regardless the number of SLN removed.

Conclusion In patients with no initial node involvement, negative SLN after NAC allows to safely avoid an ALND. Residual breast tumor and lympho-vascular invasion after NAC allow identifying patients with initially involved node with a low risk of ALND involvement.

Keywords Breast cancer · Neo-adjuvant chemotherapy · Sentinel lymph node · False negative rate · Axillary lymph node dissection

Introduction

Sentinel lymph node (SLN) biopsy is aimed at safely reducing the rate of unnecessary axillary lymph node dissection (ALND) by identifying patients with negative SLN [1, 2]. ALND is considered for cases of mapping failure or SLN involvement. Whilst initially developed in the adjuvant situation, SLN detection remains beneficial after neo-adjuvant chemotherapy (NAC) as it reduces the rate of unnecessary ALND. After NAC almost 60% of patients are free of nodes metastasis [3]. For patients with involved axillary nodes before NAC, almost 22–41% are down-staged to a negative axilla after NAC, and is even higher in patients treated with anti-HER2 therapy [4–6]. For patients treated with NAC associated with Trastuzumab and Pertuzumab, the pathological complete response rate (pCR) is within the range of 45.8% [7].

The accuracy of SLN detection after NAC remains controversial. Lymphatic drainage from breast tumors to regional nodes could be impaired by NAC, leading to a

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decrease in the SLN identification rate (IR) and an increase in the false negative rate (FNR) [8]. A meta-analysis of SLN detection after NAC has shown an IR of 90% [9]. An unplanned analysis of patients from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B27 trial, including patients with an unknown axillary status before NAC, has shown a 10% SLN FNR [10]. Considering patients with an initially proven axillary node involvement before NAC, a recent meta-analysis showed a pooled IR of 91%, and a pooled FNR of 13% [11].

Currently, the main question concerning SLN after NAC is not its feasibility but its accuracy and safety. After NAC, unlike in the adjuvant situation, SLN FN case is by definition drug resistant and may results in a higher risk of relapse. The clinical risk of SLN FNR after NAC including long-term follow-up of a large prospective multi-institutional series of patients treated with SLN alone after NAC, are almost unknown, especially in the group of patients with initially proven node involvement before NAC. A recent meta-analysis of 9 cohorts including 4125 patients treated with breast conserving therapy after NAC showed a 10% risk of loco-regional relapse within 10 years from diagnosis [12]. In this meta-analysis, almost all patients underwent an ALND, especially those with initially involved axilla. Involved nodes before NAC was shown to be associated with an increased 10 years risk of loco-regional relapse [12]. The 2014 American Society of Clinical Oncology recommendations considered as unacceptable the reported FNR of SLN after NAC, in patients who present with involved axillary nodes [13]. The 2017 update specified that recommendations for performing SLN after NAC for women with an operable breast cancer had a moderate strength and an intermediate evidence quality [14]. Recently, the Saint Gallen conference panel concluded that, for patients who presented with a clinically positive axilla down-staged to a clinically negative axilla after NAC, SLN after NAC could be adequate only for patients with at least 3 or more negative SLNs [15]. It is important to note that the median number of SLNs usually removed is 2 [16]. In the ACOSOG Z011 trial, 43% of the patients had 2 or less SLN removed following NAC [6].

The GANEA 2 (Ganglion sentinel apres chimiotherapie NEoAdjuvante) trial was a prospective multi-institutional French cohort aimed at assessing the accuracy and safety of SLN biopsy after NAC for patients treated for an operable breast cancer.

Methods

The GANEA 2 trial was approved by the national scientific committee and was registered with ClinicalTrials.gov (Number NCT01221688). Informed consent was obtained from each participating patient.

Eligibility

Patients enrolled were women aged 18 years or older, with biopsy proven primary infiltrative breast cancer, clinical stage T1 to T3, N0 to N2, M0 according to the American joint committee on cancer staging manual sixth edition (AJCC), and with a planned NAC [17]. Exclusion criteria included prior ipsilateral axillary surgery, lack of axillary assessment before NAC, pregnancy or no effective contraceptive method, and clinical T4 or N3 or M1 patients.

Treatment

Before NAC, patients underwent axillary clinical staging, axillary ultrasound assessment (AUS), and a fine needle aspiration of suspicious nodes to assess their involvement. A node was considered suspicious if it was larger than 1 cm, with irregular cortical thickening, and loss of fatty hilum. Patients without a cytologically proven axillary involvement before NAC were allocated into the cN0 group. Patients with a cytologically proven axillary involvement before NAC were allocated into the pN1 group.

The NAC regimen was left to the discretion of each participating team.

After NAC, breast and axillary surgery were performed during the same procedure, 4–6 weeks after completion of NAC. Breast surgery could be lumpectomy or mastectomy.

A combined SLN detection method with blue dye and radiocolloïd was recommended. A SLN could be blue and/or hot, identified during surgery with a blue lymphatic channel and/or a gamma probe. Patients with two or less SLN were not excluded from the trial.

After NAC, patients allocated into the cN0 group underwent a SLN biopsy and a complementary ALND only in cases of SLN mapping failure or SLN involvement (micro or macro-metastasis), and patients allocated into the pN1 group underwent a SLN biopsy and a mandatory ALND.

After NAC and surgery, patients underwent whole breast radiotherapy in cases of lumpectomy, or chest wall radiotherapy in cases of mastectomy. No direct axillary radiotherapy was delivered.

Post-surgery follow-up information was not taken into account for patients from the pN1 group. Patients from the cN0 group treated with a SLN detection alone, were followed for 3 years. This follow-up included general and clinical assessment every 6 months, and a yearly bilateral mammography. A specific clinical report form was validated with the definition of metastasis, axillary ipsilateral relapse, loco-regional relapse, breast relapse, or death.

Pathology

No intra operative pathological examination was performed. SLNs were sent to the pathology department separately from ALND specimens. Paraffin embedded SLNs were serially sectioned and stained with hematoxylin and eosin (HE). If no metastasis was detected, further immuno-histo-chemical (IHC) analysis was performed. The size of the largest nodal metastasis was recorded using the definition of the AJCC staging system 6th edition [17]. SLNs with metastasis of any size were considered positive including those only detected by IHC. Nodes from ALND were bi-sected and HE stained. A positive ALND node corresponded to a macro-metastasis (> 2 mm).

Statistical analysis

Sample size determination

The primary outcome was the SLN FNR for patients from the pN1 group with remaining positive nodes after NAC. In order to achieve a binomial Wald 95% confidence interval (CI) 10–20% if observed FNR = 15%, we required 196 assessable patients. In the GANEA 1 study, the SLN detection rate was 90.1 and 26.6% of patients with detected SLNs remained node positive after NAC [18]. Assuming 10% non-assessable patients, we had to include $= 196 \times \frac{1}{0.901} \times \frac{1}{0.90} = 242$ patients remaining node positive after NAC. Considering the rate of node involvement from the GANEA 1 study, to obtain a total of 242 patients remaining node positive after NAC, $242 \times \frac{1}{0.266} = 910$ patients were required.

cN0 group

Patients from the cN0 group, treated with a SLN biopsy alone, were followed from the time of surgery to the time of the first event or the last visit (censored). Any breast relapse, axillary relapse, distant metastasis, other cancer or death were considered as an event. Overall and event-free survival curves were calculated using the Kaplan–Meier method. Median follow-up was calculated by the inverse Kaplan–Meier method.

pN1 group

The SLN FNR (primary endpoint) was only measurable in the pN1 group where patients underwent a mandatory SLN and ALND. A FN case was defined as a patient with a successful mapping, SLN(s) without any metastasis, and a metastasis in at least one node from the ALND. The FNR was the ratio of the number of FN cases to the total number of patients with at least one lymph node involved, sentinel or not. The FNR 95% confidence interval (CI) was calculated.

The secondary objective was to determine predictive factors for positive ALND in cases of negative SLNs in patients from the pN1 group. Univariate analysis assessed the factors associated with an event by means of Chi^2 test (or Fisher's exact test) for qualitative variables, and Student's *t*-test (or Mann–Whitney test) for quantitative variables. Factors with $p < 0.15$ at the univariate step were introduced into a multivariate logistic regression model. A backward selection procedure was performed. The area under the curve (AUC) of the ROC curve was calculated, and Goodness-of-fit was verified by the Hosmer–Lemershow test. Sensitivity analyses were conducted to test the robustness of the final model by imputing missing data according to the maximum bias hypothesis (i.e., for binary variables remaining independent predictors in the multivariate analysis, the AUC of the ROC curve was recalculated after having coded all missing values either in 0 or in 1).

As there was no possibility to carry out an external validation, an internal cross-validation using a 1000-bootstrap-adjusted AUC calculation was performed using rms R package.

A bilateral formulation was chosen for all tests and a value of $p < 0.05$ was considered significant. All calculations were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.3.1 (The R Foundation for Statistical Computing).

Role of the funding source

The funder assumed costs of the trial and had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

From July 2010 to July 2014, 957 patients were included from 17 French institutions (Fig. 1). Patient characteristics are listed in Table 1.

cN0 group

606 patients were allocated into the cN0 group, and 589 were eligible for the SLN procedure (Fig. 1). Most of patients were T2 (450/589, 76.4%), HER2 negative (493/589, 83.7%), with no lympho-vascular invasion (524/589, 89.0%) (Table 1). 165 patients had no residual tumor (28.0%) and the status was unknown for 32 patients (5.4%). At least one

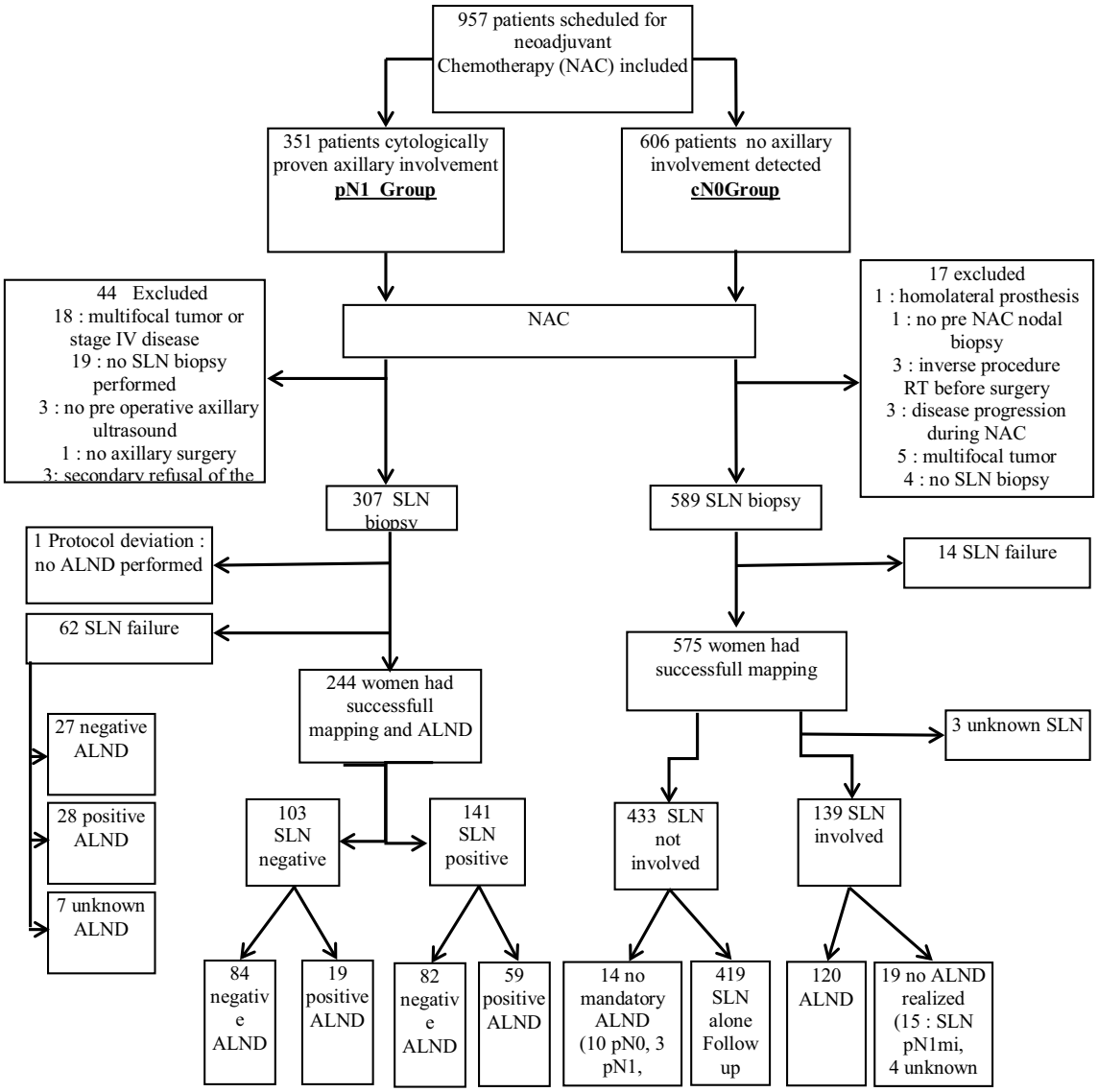

Fig. 1 GANEA 2 study flow chart. *SLN* sentinel lymph node, *ALND* axillary lymph node dissection, *NAC* neo-adjuvant chemotherapy, *pN0* not involved node at pathology, *pN1* involved node at pathology, *pN1mi* micro-metastasis identified at pathology

SLN was detected in 575 of the 589 patients (IR = 97.6%, 95% CI 96.0–98.7%). A median of two SLNs were detected (IQR 1–2, range 1–6). 212 of these 575 patients had only one SLN detected (36.9%). A SLN involvement was found in 139/572 patients (24.3%).

A subgroup of 419 patients from the cN0 group, treated with SLN alone, was followed-up as part of the study. The median follow-up was 36 months (95% CI 34–37). During the follow-up, 11 events and 10 deaths occurred. Events were 7 loco-regional relapses (3 breast ipsilateral relapse, 3 breast contralateral relapse, and 1 axillary relapse), 3 distant relapses and 1 other cancer. The overall 3-year survival was 97.2% (95% CI 94.7–98.5) (Fig. 2), and the 3-year event-free survival was 97.8% (95% CI 95.4–98.9).

pN1 group

351 patients were allocated into the pN1 group. After completion of the NAC courses, all but one of the 307 eligible patients underwent both SLN detection and ALND. Their characteristics are listed in Table 1. Most of patients were T2 (211/307, 68.7%), HER2 negative (237/307, 77.2%), with no lympho-vascular invasion (229/307, 74.3%). Eighty patients had no residual tumor (26.1%), and the status was unknown for 27 patients (8.7%).

At least one SLN was detected in 244 of these 307 patients (IR 79.5%, 95% CI 74.5–83.9%). Of these 244 patients, 96 had only one SLN detected (39.2%). A median of two SLNs were detected (interquartile range (IQR) 1–3,

Table 1 Characteristics of patients after NAC

	pN1 group $N=307$		cN0 group $N=589$	
	No	%	No	%
Age, years median	52	–	47	–
[IQR/range]	[44–61/29–85]		[40–56/24–80]	
Clinical T stage at presentation[a]				
T1	14	4.6	33	5.6
T2	211	68.7	450	76.4
T3	78	25.4	105	17.8
T4	3	1.0	0	0.0
Unknown	1	0.3	1	0.2
Clinical N stage at presentation[a]				
N0	56	18.3	509	86.4
N1	231	75.2	77	13.1
N2	20	6.5	2	0.3
Unknown	0	0.0	1	0.2
Breast tumor size after NAC, mm median	16		10	
[IQR/range]	[0–35/0–110]		[0–20/0–120]	
Breast tumor size after NAC				
No residual tumor	80	26.1	165	28.0
1–4 mm	30	9.8	52	8.8
5 + mm	170	55.4	340	57.9
Unknown (> 0 mm)	27	8.7	32	5.4
Tumor histology				
Ductal invasive	282	91.8	540	91.7
Lobular invasive	14	4.6	34	5.8
Other	11	3.6	15	3.5
SBR pathologic grade[b]				
1	5	1.6	19	3.2
2	142	46.3	253	43.0
3	154	50.1	314	53.3
Unknown	6	2.0	3	0.5
Hormone receptor status				
RH+	141	45.9	262	44.4
RH dissociated	66	21.5	84	14.3
RH−	99	32.3	243	41.3
Unknown	1	0.3	0	0.0
HER2 status[c]				
Negative	237	77.2	493	83.7
Positive (3+)	65	21.2	90	15.3
Unknown	5	1.6	6	1.0
Triple receptor negative				
Yes	70	22.8	206	35.0
No	234	76.2	382	64.8
Unknown	3	1.0	1	0.2
Lympho-vascular invasion				
Yes	73	23.8	65	11.0
No	228	74.3	524	89.0
Unknown	6	1.9	0	0.0
NAC regimen[d]				
Like FEC + taxane	237	77.2	488	82.9
Like FEC only	7	2.3	12	2.0

Table 1 (continued)

	pN1 group $N=307$		cN0 group $N=589$	
	No	%	No	%
Taxane + other	48	15.6	68	11.5
Taxane only	13	4.2	1	0.2
Other	1	0.3	1	0.2
Unknown	1	0.3	0	0.0
No. of NAC courses median	6	–	6	–
[IQR/range]	[6–7/2–10]		[6–8/3–14]	

pN1 patients with cytologically proven involved node before NAC, *cN0* patients without cytologically proven involved node before NAC, *IQR* interquartile range

[a]TNM: TNM classification system 2009

[b]SBR: Scarff Bloom Richardson grading system modified by Elston Ellis

[c]HER2 status assessed by IHC (3+)

[d]FEC: fluorouracil-epirubicine-cyclophosphamide

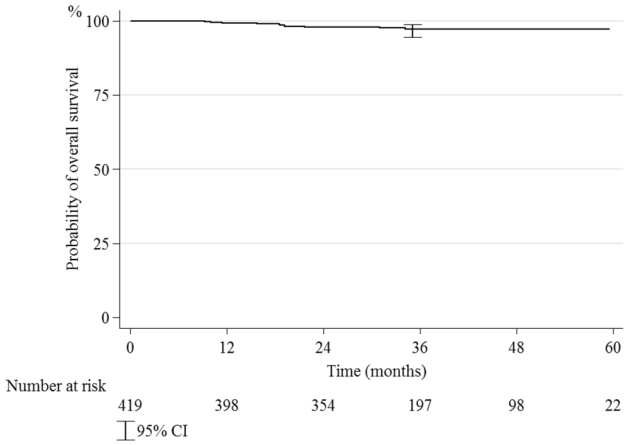

Fig. 2 Overall survival in 419 cN0 group patient treated with SLN alone. *SLN* sentinel lymph node

range 1–8). Among the 244 patients with detected SLNs and systematic ALND performed, 141 had at least one involved SLN (114 macro-metastasis, 46.7%; 27 micro-metastasis or isolated cells, 11.1%) and 103 had a tumor free SLN (42.2%). Metastatic non SLNs were found in the ALND of 59/141 patients with at least one involved SLN (41.8%).

Axillary response and observed FNR

Of the 244 women with successful mapping and ALND, the complete axillary pathological global response rate was 34.4% (84/244) (95% CI 28.4–40.4%). Of the 160 patients with involved nodes, 19 had a negative SLN and positive complementary ALND corresponding to an overall FNR of 11.9% (19/160, 95% CI 7.3–17.9%) (Fig. 1). The observed FNR was 19.3% (11/57) (95% CI 10.0–31.9%) for cases of one resected SLN versus 7.8% (8/103) for cases of two or more SLNs (95% CI 1.3–16.9%) ($p=0.041$).

Risk of complementary positive ALND in SLN negative patients

The multivariate logistic regression analysis performed on the 103 patients with no involved SLN showed that residual breast tumor size ≥ 5 mm after NAC (OR 12.32, 95% CI 2.44–62.22, $p=0.002$) and lympho-vascular invasion (OR 6.33, 95% CI 1.06–37.78, $p=0.043$) remained independent predictors for complementary involved ALND (Table 2). The number of SLNs removed did not remain as an independent predictor for complementary involved ALND. The model AUC was 0.836 (95% CI 0.735–0.937) (Fig. 3). Using these parameters, we could split the negative SLN patients group into two subgroups. In the subgroup of 54 patients with a negative SLN, a residual breast tumor size < 5 mm after NAC and no lympho-vascular invasion, the rate of positive complementary ALND was 3.7% (2/54, 95% CI 0.4–12.7%); whereas in the subgroup of 38 patients with a negative SLN, and a residual tumor size ≥ 5 mm after NAC and/or a lympho-vascular invasion, the rate of positive complementary ALND was 42.1% (16/38, 95% CI 26.3–59.2%, $p<0.0001$).

Internal cross-validation showed a 1000-bootstrap-adjusted AUC of 0.834 and sensitivity analyses performed by imputing missing data of the explanatory variables verified the robustness of the model (Online Appendix).

Discussion

Considering patients with no initially involved nodes before NAC, the current study confirmed the safety of carrying out a SLN biopsy alone after NAC, thus safely avoiding

Table 2 Factors related with risk of positive complementary ALND if negative SLN in the pN1 group ($n = 103$)

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Age (years)						
< 40 versus 40+	0.59	0.12–2.84	0.509	–	–	–
Residual tumor on surgical specimen[a]						
5 + mm versus < 5 mm	18.57	3.90–88.38	0.0002	12.32	2.44–62.22	0.002
Lympho-vascular invasion						
Yes versus no	15.75	3.57–69.34	0.0003	6.33	1.06–37.78	0.043
SBR grading						
3 versus 1 + 2	1.01	0.34–2.94	0.991	–	–	–
Triple negative status						
Yes versus no	0.85	0.46–1.55	0.590	–	–	–
Number of SLN removed						
> 1 versus 1	0.60	0.22–1.64	0.321	–	–	–

Odds ratios (OR) are presented with their 95% confidence interval (CI) and the *p*-value

SLN sentinel lymph node, *ALND* axillary lymph node dissection, *SBR* Scarff Bloom Richardson

[a]Values were missing for 13 patients

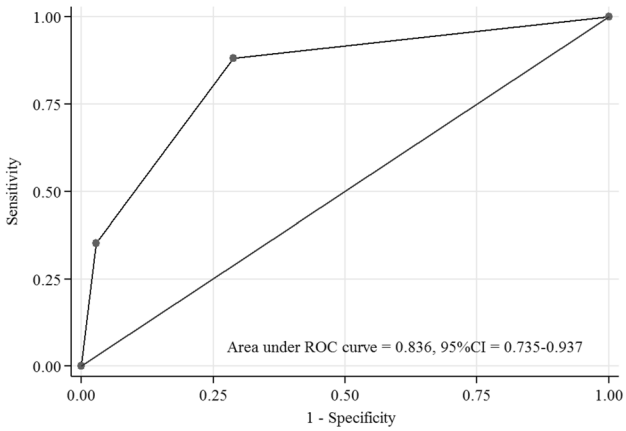

Fig. 3 Multivariate model ROC curve for predicting complementary ALND if post-NAC negative SLN [$n = 103$ patients with pre NAC cytologically positive node(s)]. *ALND* axillary lymph node dissection, *NAC* neo-adjuvant chemotherapy, *SLN* sentinel lymph node

unnecessary ALND. For patients with initially proven node involvement before NAC, the post-NAC combination of SLN results, lympho-vascular invasion and remaining breast tumor size allowed to define, for SLN negative patients after NAC, a subgroup of patients with a low risk of non SLNs involvement.

Patients with no initially involved node found before NAC

To our knowledge the GANEA 2 trial is the largest prospective multi-institutional study with a structured policy of follow-up of patients with no previous axillary involved node, treated after NAC by SLN biopsy alone, without ALND, in cases of SLN free of metastasis. In a recent retrospective mono-institutional series of 181 patients with an initially negative axilla, treated with SLN alone after NAC for a T0–T3 breast cancer, no patients experienced an axillary relapse after a median follow-up of 51.1 months [19]. Considering the results of the current study this strategy appears to be accurate and safe with one axillary relapse among 419 patients after a median follow-up of 3 years.

Patients with initially involved nodes before NAC

In this group of patients who are at high risk of involved nodes after NAC, the main objective is to reduce the risk of a SLN FN result. In the current study, the overall SLN FNR was 11.9% for this group of patients.

The SLN FNR varies according to the number of SLNs removed. Our FNR was 19.3% for cases of only one SLN removed. In the ACOSOG Z1071 trial, the FNR was 21% for cases of two or less SLNs removed [6]. In SENTINA trial Arm C, the FNR was 24.3% for one SLN removed and 18.5% for two [20]. The proportion of patients with only one SLN removed was 24% (142/592) and 12% (86/689) in the Sentina trial and ACOSOG Z1071 trial respectively. The number of SLNs removed is variable and cannot be anticipated or imposed. Selection of patients, who could be spared an unnecessary ALND with a low risk of failure, should be independent from the number of SLNs removed.

The SLN FNR varies according to the use of IHC. In the current study IHC was part of the pathological analysis. In the FNAC trial, IHC was mandatory, allowing micro-metastatic SLNs to be characterized as a positive SLN. The FNR was reduced from 13.3% without IHC to 8.4% with IHC [21]. In a recent meta-analysis, the FNR was lower for

cases of combined IHC and HE staining compared to HE staining alone, (8.7% vs. 16%, $p = 0.001$) [22].

The FNR varies according to the pathological response to NAC. We previously showed that FN cases after NAC were found in patients with involved nodes with or without pathological evidence of a therapeutic effect [18]. In a prospective database from the MD Anderson, 237 patients with documented biopsy proved N1 before treatment, the rate of axillary pathological complete response was linked with the rate of breast pathological complete response [23]. In two recent series of breast cancer patients with initially clinically positive nodes treated with NAC, high nuclear grade, human epidermal growth factor receptor 2-positive, negative estrogen or progesterone receptor tumors were more likely to achieve nodal pathological complete response. Nomograms were built for predicting axillary complete response to NAC with an area under the ROC curve of 0.77 and 0.787 [24, 25]. In a series of 104 patients treated with NAC, with involved SLNs and ALND after NAC, the risk of non-SLN involvement was significantly linked with initially involved axillary nodes, lympho-vascular invasion, and pathologic breast tumor size at surgery allowing to build a nomogram to predict the risk of remaining non-SLN involved after NAC with a bootstrap-adjusted AUC of 0.762 [26]. In the current study, the multivariate logistic regression analysis performed on patients with initially involved nodes before NAC and no involved SLN after NAC showed that residual breast tumor size ≥ 5 mm after NAC and lympho-vascular invasion remained independent predictors for complementary involved ALND (AUC of the ROC curve = 0.834). In cases of residual breast tumor < 5 mm, no lympho-vascular invasion and no involved SLN, a patient could avoid a complementary axillary surgery regardless of the number of resected sentinel nodes, with a 3.7% risk of remaining non-SLN involved. Considering the definition of cut-off of 5 mm of remaining breast tumor after NAC, we observed no lymph node involvement after NAC in the subgroup of 103 patients an initially involved node, with a negative SLN after NAC and less than 3 mm of residual breast tumor. This strategy does not depend on the number of resected SLNs.

The pathological status of initially involved nodes after NAC highly reflects the pathological status of the whole axilla. In a recent prospective series of 118 patients with the initially involved node tagged before NAC and resected after NAC within the SLN specimen and a complementary ALND, the SLN FNR decreased from 10.1 to 1.4% [27]. Residual nodal disease after NAC was found in the tagged node in 95.8% of cases. Several innovative methods have been published to retrieve this targeted node after NAC, such as marking the axillary lymph node with iodine-125 (MARI), black charcoal or wire localization [28, 29]. Targeting this node before NAC regardless of the method used, must be considered as an additional invasive procedure for the patient.

Limitations of the study

The current study has several limitations.

Considering the number of patients required in the pN1 group with remaining involved node after NAC, we calculated a total of 910 patients were required to enter the study in order to obtain a total of 242 pN1 patients after NAC. Unfortunately, despite including 40 more patients than statistically required (957 vs. 910 needed), more patients had node involvement down-staged by NAC when compared to the GANEA 1 study, resulting in less pN1 patients after NAC (160 vs. 242 needed) [18]. Due to financial considerations we have been forced to stop study recruitment.

The model predicting the risk of a complementary involved ALND in the group of patients with a non-involved SLN was performed on an internal sample without an external validation.

Another limitation is the potential need for a two steps surgical strategy. Surgeons should collect information regarding the SLN status, lympho-vascular invasion and the remaining breast tumor size, in order to decide whether or not to perform a complementary ALND. It could be performed during the same surgical procedure, which could require an intra operative pathological assessment, or during a second surgical procedure based on definitive pathological results. Patients with negative SLNs, no lympho-vascular invasion and breast tumor size ≤ 5 mm could avoid a complementary ALND with a low risk of persistent non-SLN involvement.

Conclusion

Early breast cancer patients treated with NAC with no initially involved nodes and with a negative SLN after NAC could safely be spared an unnecessary lymphadenectomy with a low risk of relapse. For patients with an initially involved axillary node before NAC, the challenge is to accurately select post-NAC negative SLN patients with the lowest risk of leaving involved axillary non-sentinel nodes. The current study allowed a new strategy to be defined for selecting patients who could safely avoid a complementary axillary lymphadenectomy with a low risk of an inappropriate selection.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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