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ORIGINAL REPORT

Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy for Advanced Breast Cancer: Results of Ganglion Sentinelle et Chimiothérapie Neoadjuvante, a French Prospective Multicentric Study

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ABSTRACT

Purpose
To determine the detection rate, the false-negative rate, and the accuracy of sentinel lymph node (SLN) detection after neoadjuvant chemotherapy (NAC) for advanced breast cancer.

Patients and Methods
A prospective multicentric study was initiated to evaluate the results of SLN biopsy with the combined method after NAC for advanced large operable breast cancer.

Results
From September 2003 to March 2007, 195 patients enrolled from 12 institutions were found suitable for evaluation. The detection rate was 90% (176 of 195 patients), and the false-negative rate was 11.5% (six of 52 patients). Patients without axillary palpable nodes (N0) before NAC had a better detection rate compared with patients with axillary suspicious nodes (N1, 94.6% *v* 81.5%; $P = .008$). The false-negative rate was not correlated with clinical nodal status before NAC (9.4% *v* 15%; $P = .66$).

Conclusion
This study confirms the feasibility of SLN biopsy after NAC in the case of large operable breast cancer. The detection rate, false-negative rate, and accuracy do not differ from those obtained in the case of early breast cancer without NAC, thus demonstrating the feasibility of SLN biopsy after NAC.

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INTRODUCTION

Sentinel lymph node biopsy (SLNB) has become a validated technique that has replaced axillary lymphadenectomy for axillary staging in patients treated for an early breast cancer and is associated with less morbidity.[1-3]

Over the past decade, neoadjuvant chemotherapy (NAC) has become increasingly common for the treatment of operable large breast cancer, the main objective being breast-conserving surgery.[4-6]

After NAC, the standard surgical treatment consists of residual breast tumor resection and axillary level I to II lymphadenectomy to improve local control.[7] In this case, 50% to 58% of patients have negative axillary lymph nodes.[8] NAC downstages 20% to 40% of pretherapy documented axillary metastatic lymph nodes, with a complete pathologic response in 32%.[6,9,10]

Sparing patients treated with NAC the morbidity of a lymphadenectomy, if possible, would be advantageous. This objective raises the question of both the feasibility and accuracy of the SLNB procedure after NAC.

Unfortunately, among the published series, several have provided results that are not consistent with the validation of this strategy as a result of a low detection rate ($\leq$ 85%) and a high false-negative rate (from 22% to 33%).[11-13] In fact, SLNB is not recommended for axillary staging of patients receiving NAC.[14]

Until now, the question of SLNB accuracy after NAC has been addressed mostly through small, retrospective, single-institution series with a heterogeneous clinical indication and no specific detection methods, leading to significant variability in detection and false-negative rates.

To assess the accuracy of SLNB after NAC, we performed a large prospective multi-institutional study with homogeneous clinical indications, specific detection methods, and specific pathologic analysis methods.

PATIENTS AND METHODS

The Ganglion Sentinelle et Chimiothérapie Neoadjuvante (GANEA) study was validated by scientific and ethical boards as a prospective multi-institutional study with conservative breast surgery, SLNB, and level I to II axillary lymphadenectomy after NAC for large operable breast cancer. Informed consent was obtained from all patients. Each team that included patients in this study had undertaken to validate their SLNB learning curves beforehand.

Patients eligible for the GANEA study had an operable, unifocal, noninflammatory, large breast tumor. Infiltrative carcinoma had to be diagnosed before treatment by core needle biopsy. Axilla could be clinically free of nodes (N0) or with only movable, palpable nodes that were not fixed together (N1). NAC was proposed to enable the patient to be eligible for breast-conserving surgery. Each patient had to be treated with NAC, and the first surgical procedure had to be breast conserving at the time of SLNB and axillary lymphadenectomy.

Exclusion parameters were noninfiltrative cancer, inflammatory cancer, clinical fixed axillary lymph nodes, previous breast surgery, mastectomy at the time of SLNB, or a premature interruption of NAC for cancer progression.

Lymphatic Mapping Procedure

Sentinel lymph node (SLN) detection was always performed with the combined method. Injection sites were superficial within the parenchyma around the tumor or subareolar, left to the discretion of the participating surgeons.

The radio detection method used unfiltered technetium-99m–labeled rhenium sulfide colloids (Nanocis kit; Cis Bio International, Saclay, France). The intraoperative detection protocol for each patient included, successively, counts for background activity and counts for each axillary SLN, and ended with control of the lack of activity in the axilla after SLN resection.

For colorimetric detection, 2 mL of patent blue was injected under general anesthesia. The SLN was defined by intraoperative detection of a number of counts per second at least twice that of the background level and/or blue node staining. After SLNB, all patients underwent a level I to II axillary lymphadenectomy.

Pathologic Analysis

No intraoperative histopathologic examination was performed. SLNs were submitted by the surgeons separately from the rest of the axillary lymphadenectomy.

Each node (sentinel and nonsentinel) was serially sectioned and totally embedded in paraffin. SLNs were cut into six sections at 150-μm intervals.

Standard staining was performed on three levels, and immunohistochemical labeling was performed at the three intermediary levels in the absence of metastatic disease detected on these first sections. The nonsentinel lymph nodes obtained by lymphadenectomy were totally included with 4-μm section cuts from each block and stained with hematein phlostin safron. No immunohistochemical labeling was performed for the nonsentinel lymph nodes.

The microscopic reporting stated the number of axillary SLNs, the total number of nodes, and the number of nodes containing macrometastasis ($>$ 2 mm) and micrometastasis (0.2 to 2 mm) using the definition of the last American Joint Committee on the Cancer staging system.[15]

The histologic features of the therapeutic effect on breast tumor and lymph nodes were evaluated according to the scale established by Sataloff et al,[16] graded from A to D, as follows: for the breast tumor (B), total or near-total therapeutic effect (BA), more than 50% therapeutic effect (BB), less than 50% therapeutic effect (BC), and no therapeutic effect (BD); and for lymph nodes (N), no metastatic disease and evidence of a therapeutic effect (NA), no metastatic disease and no therapeutic effect (NB), metastatic disease and therapeutic effect (NC), and metastasis and no therapeutic effect (ND).

Studied Parameters

Clinical breast tumor size and axilla assessment were obtained before any treatment by physical examination. The detection rate was defined as the number of patients whose axillary SLN was isolated in relation to the total number of patients included.

The false-negative rate was defined as the ratio of the number of patients with a false-negative case of SLNB to the number of patients with at least one involved node ($>$ 2 mm), SLN or not, among patients with at least one detected SLN. The results of the detection rate and false-negative rate were stratified according to clinical axillary involvement before treatment using the latest American Joint Committee on Cancer staging system and in accordance with the Sataloff grading.[16] Accuracy was defined as the ratio of the number of patients for whom SLNB correctly predicted axillary lymph node status to the number of patients with at least one detected SLN. The average number of SLNs collected was calculated according to the SLN definition.

Statistical Considerations

To demonstrate that the expected false-negative rate of approximately 10% was accurate to $\pm$ 5% with $\alpha = 5\%$, 139 patients had to be included to achieve 95% certainty. Statistical analyses were performed to compare the detection rate and false-negative rate according to clinical axillary involvement before treatment and Sataloff grading of pathologic response to treatment using the χ^2 test or Fisher's exact test if necessary.

RESULTS

Patient Populations and Characteristics

From September 4, 2003, to March 28, 2007, 227 patients were prospectively included from 12 institutions. Of these patients, 195 patients were suitable for evaluations. A consort diagram illustrates the study group in Figure 1. Patients characteristics are listed in Table 1.

In our study, there was neither a standard chemotherapy nor a standard number of chemotherapy cycles. Precisely, 23% of the patients had an anthracycline-based NAC regimen, 70% had a taxane-based NAC regimen (combined with anthracyclines for half), and 7% had other types of NAC regimens. The median number of NAC cycles was 6.7 (standard deviation = 2).

SLN Detection Rate

The results of the SLN detection success rates are listed in Table 2. The mean number of resected SLNs was 1.9 (range, one to six SLNs). The mean number of resected nodes, SLN or not, was 12.3 (range, three to 26 nodes).

SLN Pathologic Results

The pathologic results for lymph nodes are listed in Table 3. The average rate of patients with at least one involved node, sentinel or not, was 26.6% (52 of 195 patients). The false-negative rate was 11.5% (six of 52 patients; Table 2). For patients with an involved sentinel node, no

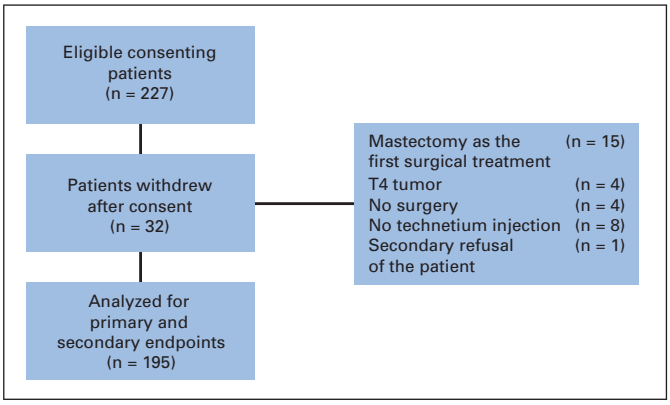

Fig 1. CONSORT diagram.

Table 1. Patient Characteristics: Pretherapy Characteristics Before Neoadjuvant Chemotherapy

Characteristic	No. of Patients
No. of patients	195
Clinical size of tumor	
T0	2
T1	6
T2	149
T3	38
Lymph node status	
N0	130
N1	65
Pathologic subtype	
Ductal	166
Lobular	23
Other	6
SBR pathologic grade	
1	19
2	83
3	82
Unknown	11
Hormone receptor status	
Positive	123
Negative	72
Basal-like	64

Abbreviation: SBR, Scarff-Bloom-Richardson.

other involved node was found in the lymphadenectomy in 26 cases (26 of 46 patients, 56.5%; Table 3). In the case of the six patients with false-negative SLN results, five patients had only one involved node, and the sixth patient had two involved nodes. Fifteen patients had a micrometastasis in the SLN without another involved node, SLN or not.

Regarding the 130 patients with N0 disease, mapping was successful in 123 patients and unsuccessful in seven patients. Among patients for whom mapping was successful, 27 patients had a macrometastasis in the SLN, with macrometastasis in the non-SLN in 15 patients; 10 patients had a micrometastasis in the SLN, with macrometastasis in the non-SLN in three patients; and 86 patients had noninvolved SLNs, with a macrometastasis in the non-SLN in three patients. Among the seven patients for whom mapping was unsuccessful, three patients had non-SLN macrometastasis.

Regarding the 65 patients with N1 disease, mapping was successful in 53 patients and unsuccessful in 12 patients. Among patients for whom mapping was successful, 15 patient had a macrometastasis in the SLN, with a macrometastasis in the non-SLN for eight patients; seven patients had a micrometastasis in the SLN, with a macrometastasis in the non-SLN for one patient; and 31 patients had a noninvolved SLN, with a macrometastasis in the non-SLN for three patients. Among the 12 patients for whom mapping was unsuccessful, six patients had non-SLN macrometastasis.

Table 3. Pathologic Results in Lymph Nodes

Patients With Macrometastasis	No. of Patients
Both in SLN and lymphadenectomy (non-SLN)	20
1 non-SLN involved	7
2 non-SLNs involved	7
3 non-SLNs involved	2
> 3 non-SLNs involved	4
In SLN only	26
In lymphadenectomy only	6
Total	52

Abbreviation: SLN, sentinel lymph node.

Accuracy was 96.5% (170 of 176) in the whole population, 97.5% (120 of 123) in patients with N0 disease, and 94% (50 of 53) in patients with N1 disease ($P = .37$).

Detection rates and false-negative rates varied with the response to the treatment at the tumor or the nodes according to Sataloff grading. Regarding the breast tumor, the detection rate was 88% (59 of 67) for BA, 90% (53 of 59) for BB, 93.6% for BC (44 of 47), and 95% (19 of 20) for BD, and the false-negative rate was 66% (two of three) for BA, 10% (two of 20) for BB, 9.5% (two of 21) for BC, and 0 (0 of eight) for BD.

Regarding nodes, the detection rate was 84% (37 of 44) for NA, 97% (75 of 77) for NB, 86% for NC, and 89.6% (26 of 29) for ND, and false-negative rate was 0 (0 of 37) for NA, 0 (0 of 75) for NB, 8% (three of 37) for NC, and 11.5% (three of 26) for ND. Two patients were not classified according to Sataloff grading. Results of false-negative rate according to Sataloff grading and axillary clinical evaluation are summarized in Table 4.

DISCUSSION

It is currently debatable whether SLNB can accurately predict axillary lymph node status after NAC. The main hypotheses to explain axillary mapping failures after NAC are an alteration of the lymphatic pathway owing to fibrosis of lymphatic channels, the potential obstruction of lymphatic channels with cellular material or tumor emboli, fibrosis of lymph vessels, and a fatty degeneration owing to the apoptosis of tumor cells.[17,18]

To avoid difficulties resulting from pathologic modifications of the lymphatic pathway secondary to NAC, some authors suggested

Table 2. Sentinel Lymph Node Detection Rate

	Detection Rate				False-Negative Rate			
Patient Group	%	No. of Patients	Total Patients	χ^2 P	%	No. of Patients	Total Patients	χ^2 P
All patients, n = 195	90.1	176	195		11.5	6	52	
N0 patients, n = 130	94.6	123	130	.008	9.4	3	32	.66
N1 patients, n = 65	81.5	53	65		15	3	20	

NOTE. N0 indicates patients with axilla clinically free of involved nodes; N1 indicates patients with clinical axillary suspicious nodes not fixed.

Table 4. Pathologic Results of Axillary Lymph Nodes According to Sataloff Grading in Patients With SLN Detected

	False-Negative Cases						
	N0		N1		Total		
Sataloff Grade	No. of False-Negatives	Total Patients	No. of False-Negatives	Total Patients	No. of False-Negatives	Total Patients	χ^2 P
NA	0	22	0	15	0	112*	.003
NB	0	61	0	14			
NC	3	25	0	12	6	63†	
ND	0	14	3	12			
MD	0	1			0	1	
Total	3	123	3	53	6	176	

Abbreviations: N, node; A, no metastatic disease and evidence of a therapeutic effect; B, no metastatic disease and no therapeutic effect; C, metastatic disease and therapeutic effect; D, metastasis and no therapeutic effect; MD, missing data.
*Total 112 patients = 22 + 61 + 15 + 14 patients with grades NA and NB.
†Total 63 patients = 25 + 14 + 12 + 12 patients with grades NC and ND.

performing SLNB before NAC.[19] According to this strategy, women with involved SLNs before NAC must undergo axillary lymphadenectomy after NAC.[20] This strategy has two main disadvantages: first, each woman with involved SLNs will experience two separate axillary surgical procedures, before and after NAC, and second, women with lymph node metastasis at presentation, eradicated by NAC, will undergo an unnecessary lymphadenectomy.[21] SLNB performed after NAC eliminates the need for two axillary surgical procedures for patients with involved sentinel nodes allows pathologic evaluation, and may avoid a systematic axillary lymphadenectomy in the case of lymph node downstaging.

To date, 25 series[9,11-13,21-37] have been published dealing with SNLB after NAC (Table 5). These previous series contain methodologic weakness. Apart from the four largest series with more than 100 patients (range, 104 to 428 patients), the average rate of inclusions was 37 patients (range, 14 to 54 patients). These series are mainly retrospective, and only three series were multi-institutional.[24,38,39] In 13 series, there was no specific protocol for SLN detection as part of the study.

When only the four largest series of 100 patients or more are considered, the results reported are detection rates ranging from 85% to 93% and false-negative rates ranging from 8% to 10.7%.[38-41] These results are comparable to the detection rate and false-negative rate of SLNB in the case of early breast cancer pooled in a recent meta-analysis.[42]

Our series showed that SLN detection with a combined method gives a detection rate of 90.2%, a false-negative rate of 11.5%, and an accuracy rate of 96.5% after NAC for patients with a large operable breast cancer. We particularly showed that SLNB results vary according to clinical pretreatment axillary status and pathologic response to NAC.

Our detection rate is similar to the pooled results of detection rates published in a recent meta-analysis of SLNB after NAC, ranging from 72% to 100%.[43] In our series, the mapping failures led to an unnecessary lymphadenectomy in only 10 of 19 patients, with no involved lymph nodes.

The methods of SLN detection have an impact on both the detection rate and the false-negative rate.[42] In our prospective series, we used the combined method. In the series by Mamounas et al[38] of 428 patients, the detection rate was 87.6% with the combined methods and 78.1% with blue dye alone.

False-negative rate assessment requires both an SLNB and a complete level I to II lymphadenectomy.[44] Our results are consistent with the 12% false-negative rate in the recent meta-analysis of SLNB after NAC and with the 9.8% results of National Surgical Adjuvant Breast and Bowel Project B32 trial.[43,45] Only three series have revealed a false-negative rate of up to 20%, with a small cohort, and in two, a low detection rate less than 90% was also noted.[11-13] In the four series with more than 100 patients, the false-negative rate ranged from 8% to 10.7%.[38-41] To reduce the SLNB false-negative rate after NAC, Yu et al[41] proposed an axillary intraoperative ultrasound assessment after SLNB to explore the nonsentinel region for additional suspicious lymph nodes, reducing the false-negative rate from 9.6% to 1.39%. In the case of patients treated for an early breast cancer, a positive preoperative positron emission tomography imaging showing suspicious axillary lymph nodes may indicate a lymphadenectomy rather than a SLNB, with a high specificity limiting the false-negative rate.[46]

SLNB detection rates vary according to clinical assessment before or after NAC.[47] The current study shows that patients with clinical N0 disease have the best detection rate ($P = .008$) as compared with patients with clinical N1 disease, with no difference in false-negative rates ($P = .66$).

The impact of pretherapy axillary lymph node assessment on false-negative rate remains controversial. In the study by Mamounas et al,[38] the false-negative rate from the National Surgical Adjuvant Breast and Bowel Project B-27 trial did not differ for patients with clinical N0 disease as compared with those with clinical N1 disease. In a recent study of patients with SLNB and axillary lymphadenectomy with suspicious axillary lymph nodes, Lee et al[47] did not find any difference in false-negative rate and accuracy when comparing the group of patients treated with NAC to the group of patients treated without NAC.

The correlation between the false-negative rate and the pathologic response to treatment is rarely studied. In a series of 54 patients with pretreatment biopsy-proven axillary metastasis, Newman et al[9] demonstrated a high SLNB accuracy after a complete or partial pathologic response to NAC. The high false-negative rate observed in the study by Shen et al[13] with a series of patients with pretreatment biopsy-proven axillary metastasis may be linked to the lack of immunohistochemical analysis. An examination of SLNs by serial sectioning and immunohistochemical staining significantly increases the detection rate of micrometastasis, which could reduce the rate of false-negative cases.[48] In the current study, we found no false-negative cases when nodes contained no metastatic disease, with

Table 5. 25 Published Series

First Author	Year	No. of Patients	Detection Method		pN+ (%)	DR (%)	FNR (%)
			Method	No. of Patients			
Breslin[22]	2000	51	Blue	23	51	84	12
			Combined	28			
Nason[12]	2000	15	Combined	15	66	86.6	33 (3/9)
Julian[23]	2001	31	Blue	1	35	93.5	0 (0/11)
			Isotope	2			
			Combined	28			
Fernández[11]	2001	40	Blue	15	45	85 (34/40)	22 (4/18)
			Isotope	1			
			Combined	24			
Tafra[24]	2001	29	Combined	29	57	93	0 (0/15)
Brady[25]	2002	14	Blue	13	77	93	0
			Combined	1			
Stearns[26]	2002	34	Blue	34	45	85	14
Miller[27]	2002	35	Blue	15	30	86	0 (0/9)
			Isotope	1			
			Combined	19			
Haid[28]	2003	45	Combined	45	NP	93	4 (1/24)
Schwartz[29]	2003	21	Blue	21	52	100	9 (1/11)
Balch[30]	2003	32	Combined	32	61	97 (31/32)	5 (1/19)
Piato[31]	2003	42	Isotope	42	43	97.6	16.7 (3/18)
Reitsamer[32]	2003	30	Combined	30	50	86.7	6.7 (1/15)
Lang[33]	2004	53	Blue	6	45.3	94	4 (1/24)
			Isotope	38			
			Combined	9			
Aihara[34]	2004	20	Blue	20		85	8
Shimazu[35]	2004	47	Combined	37	70	93.6	12.1
			Blue	3			
			Isotope	3			
			Not described	4			
Kang[36]	2004	54	Blue	9	50	72.2	11.1
			Isotope	33			
			Combined	12			
Patel[37]	2004	42	Not described	42	42	95	0
Mamounas[38]	2005	428	Blue	128	41	84.8	10.7 (15/140)
			Isotope	63			
			Combined	234			
			Not described	3			
Jones[21]	2005	36	Not described	36	53	81	11 (2/18)
Taush[39]	2006	169	Blue	29	45	85	8 (6/76)
			Isotope	20			
			Combined	120			
Kinoshita[40]	2007	104	Blue	13	38.4	93.4	10 (4/40)
			Combined	91			
Yu[41]	2007	127	Blue	127	54	91.3	9.6
Shen[13]	2007	69	Blue	5	58	92.8	25
			Isotope	7			
			Combined	57			
Newman[9]	2007	54	Blue	5	66	98	8.6 (3/36)
			Isotope	11			
			Combined	38			
Pooled data		1,622	Blue	468			
			Isotope	221			
			Combined	852			
			Not described	81			

Abbreviations: pN+, pathologic node positive; DR, detection rate; FNR, false-negative rate.

evidence of a therapeutic effect (NA) or not (NB), and six false-negative cases when nodes contained metastatic disease, with evidence of a therapeutic effect (NC) or not (ND), regardless of pretherapy clinical axillary status ($P = .03$).

In the particular case of NAC, a false-negative SLN does not lead to a risk of inadequate systemic treatment, because chemotherapy has already been performed. Systemic adjuvant treatment will not be modified by the axillary pathologic results. A false-negative result may

impact decision about postsurgical irradiation, particularly concerning the lymph node area as axillary, supraclavicular, or internal mammary areas. The potential risk of undertreatment as a result of lack of lymph node area radiotherapy remains controversial. The risk of microscopic invasion of the supraclavicular lymph nodes exceeds 15% in the case of four and more involved axillary nodes.[49] However, in our series, the SLN was the only involved node in 56.5% of patients, and in the case of the six patients with false-negative SLN results, five patients had only one involved node and the sixth patient had two involved nodes. In a recent overview of breast cancer radiotherapy, Poortmans[50] stated that no prospective trials evaluated definitively the value of regional lymph node area irradiation.

The main risk may be that of axillary relapse. In the setting of early breast cancer without NAC, axillary relapse is a rare event, occurring in approximately 2% of cases.[51] In a randomized trial with a series of 697 patients and with a false-negative rate of 16.7%, Zavagno et al[52] found only one case of axillary relapse at 56 months of follow-up.

In summary, our series is the only prospective multi-institutional series designed to address the question of the feasibility and accuracy of SLNB after NAC for large operable breast cancer. The detection and false-negative rates do not differ from those obtained in the case of early breast cancer without NAC, thus demonstrating the feasibility and accuracy of SLNB after NAC. Even in the case of clinically suspicious axilla, the false-negative rate remains acceptable, and the use of preoperative sonography or positron emission tomography imaging may reduce the rate of false-negative results.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Administrative support: Jean-Marc Classe
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Data analysis and interpretation: Jean-Marc Classe, Virginie Bordes, Loic Campion, Sylvia Giard
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