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**The predictive value of sentinel node biopsy in early breast cancer after neo-adjuvant chemotherapy: A prospective study**

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## Abstract

*Objective:* A sentinel Node (SN) has replaced axillary lymph node dissection (ALND) in patients with clinically node negative axilla (cN0). SN after Neo-adjuvant chemotherapy (NACT) is feasible but not accurate in clinically node positive (cN1-3) patients. The goal of this study is to determine the negative predictive value (NPV) of SN in cN0 breast cancer after NACT. A secondary endpoint is to determine if ALND can be avoided after NACT regardless of the pre-treatment clinical staging of the axilla, in case of a normalization of the  $^{18}\text{F}$ -fluoro-2-deoxy-glucose positron emission tomography scan (PET-CT scan).

*Design:* A single institution prospective study regarding the negative predictive value of the SN in breast cancer after NACT was conducted in the Multidisciplinary Breast Clinic of the Antwerp University Hospital from 29/03/2010 until 01/12/2015 (Study number: B30020108368). Inclusion criteria for study participation were: breast cancer, age above 18 years, female, tumor stages T2-T4 N0-3 or T1N1-N3. All patients were staged by a mammography, ultrasound of the axilla, MRI of the breast, PET-CT scan and bone scintigraphy. They received NACT consisting of 12 cycles of paclitaxel or 4 cycles of docetaxel followed by dose dense doxorubicin or epirubicin/cyclofosfamide or vice versa as a standard initial treatment. After 6 weeks, a PET-CT scan was performed for early tumor response evaluation. At the day of operation, a  $^{99\text{m}}\text{Tc}$ -labelled nanocolloid was used to identify the SN. During the surgery the SN were removed separately together with a complete ALND.

*Results:* A total of 150 patients were enrolled in our study of which 129 were eligible for analysis. 53 patients had a positive SN of which 32 have a positive axillary lymph nodes (ALN), positive predictive value (PPV) was 60%; 76 patients had a negative SN of which 6 had a positive ALN (NPV 92%). The sensitivity is 84% and the specificity 76% with a false omission rate (FOR) of 8%. In total 45 patients ALN were clinical negative and no suspect lymph nodes were seen on ultrasound, MRI and PET-CT scan) and 45 patients had negative a SN, with no ALN and 2 patients had a positive SN of which 1 patients had axillary involvement (NPV 100%). The FOR of cN1: 5%,

cN2: 37%, cN3 33%. A total of 22 patients out of 84 patients (26%) of which 15/49 cN1 (30%), 6/23 (26%) cN2, 1/12 (8%) have after 6 weeks of chemotherapy and normalization on PET-CT scan. A total of 17 patients had a negative SN and ALN. The FOR was in this group was 0%.

*Conclusion:* A SNB should become the standard after NACT if case of a cN0. If after NACT the PET CT has normalized, no ALND should be performed if the SN is negative.

Key-words:

neoadjuvant chemotherapy, sentinel node, breast cancer, axillary lymph node dissection, PET-CT

## Introduction

Axillary lymph node dissection (ALND) in patients with breast cancer had been applied as a staging procedure to determine the prognosis, select appropriate postoperative adjuvant therapy and for loco-regional control of the disease (1). In the beginning of the 1990s the concept of sentinel node (SN) was introduced. This concept of minimal invasive surgery for the axilla had fewer side effects than ALND (2-4). SN is the identification and subsequent excision of the first node(s) to which the tumour drains their lymphatic fluid (5-7). SN has been widely accepted as an accurate alternative to routine ALND for staging patients with early breast cancer (5-7). Nowadays, SN is becoming the surgical procedure of choice to predict the axillary state in clinical negative breast cancer and avoids unnecessary morbidity (3,4,7). Furthermore, new studies suggest that completion ALND after positive sentinel node does not improve outcomes in carefully selected patients (8).

Neo-adjuvant chemotherapy (NACT) is gaining interest as it offers the advantage of downstaging the disease and testing the efficacy of therapy administered to patients (9). The introduction of the platina derivatives in neoadjuvant trials with their exceptional high pathological complete response rates are challenging to rethink the optimal treatment options in early and locally advanced breast cancer (9). If it has been decided to give neoadjuvant chemotherapy based on the tumor characteristics and or LN status than SN doesn't influence the decision. Removing the SN before the start of the NACT still doesn't allow omitting axillary surgery after the NACT. The status of the axilla is important after the NACT and not before. The advantage of the NACT is that it can also downstage the axilla, thereby opening the door for lesser surgery. The SN after NACT in patients with early or locally advanced breast cancer, is still debatable. In older studies the false negative SN detection rates after NACT vary between the 8% and 20% (10,11). Until today only sentinel node biopsy is regarded not accurate after NACT.

The goal of this study was to determine the negative predictive value (NPV), and False omission rate (FOR) of the SN after NACT, regardless the clinical node-stage before

initiation of NACT. A secondary endpoint is to determine if ALND could be avoided after NACT in case of clinical negative node before NACT or after 6 weeks of treatment with normalisation of  $^{18}\text{F}$ -FDG PET-CT imaging and intra-operative negative SNB.

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## Patients and Methods

In this population-based study, we selected patients from Multidisciplinary Breast Clinic of the Antwerp University Hospital (Study number: B30020108368). The present single institution prospective study was conducted in the period between 29 Mars 2010 and 31 December 2015. Inclusion criteria were (1) female patients with invasive breast cancer; (2) women aged >18 years; (3) tumour stages cT1N1-3M0 and cT2-3N0-3M0; (4) confirmation of axillary node metastasis by fine needle aspiration cytology (FNAC); (5) all patients had received NACT as primary treatment with pre-treatment  $^{18}\text{F}$ -FDG PET-CT control; (6) confirmation of tumour negative lymph node after 6 weeks of NACT by imaging technique  $^{18}\text{F}$ -FDG PET-CT scan with or without axillary ultrasound.

### *Axillary Lymph Node Evaluation*

Physical examination and ultrasonography of the axillary lymph nodes were performed before and after NACT as previously described (12). Additionally, in order to compare the activity of the lymph nodes, all patients had received a  $^{18}\text{F}$ -FDG PET-CT scan before and after 6 weeks after NACT. Pre NACT node positivity was confirmed by combination of physical examination, cortical hypertrophy of lymph node on ultrasound (US) and FNAC (Fine Needle Aspiration Cytology).

### *Imaging Techniques*

All patients underwent ultrasound/mammography with or without magnetic resonance imaging (MRI) depending on the breast tissue density to estimate the extend of the disease and the axillary lymph node status, based on previous experience (13,14). US guided core biopsy +/- FNAC was performed on the suspected lesions. Further staging to detect possible distant metastasis was performed by ultrasound of the abdomen, lung X-ray and bone scintigraphy.

### *Neoadjuvant Chemotherapy*

All patients had received neoadjuvant chemotherapy as standard primary treatment consisting of 12 weeks of paclitaxel or 4 cycles of docetaxel (3-weekly) followed by dose dense doxorubicin or epirubicin/cyclophosphamide or vice versa. As part of study protocol,  $^{18}\text{F}$ -FDG PET-CT scans were performed before and 6 weeks the NACT in order to evaluate the tumour and node response. Based on  $^{18}\text{F}$ -FDG PET-CT findings and the clinical situation, treatment protocols of some patients could be changed if there was no tumour response.

### *Surgical Intervention*

Breast-conserving surgery or mastectomy, was performed on the primary breast tumour followed by SN and ALND regardless the histopathological intra-operative examination of the SN. At the day of operation, all the patients had a preoperative injecting with a  $^{99\text{m}}\text{Tc}$ -labelled nanocolloid in the peri-areolar region. A gamma detector was used to localize the SN(s) preoperative and aids the excision of all radioactive SN(s) intra-operative. In some cases of difficult preoperative SNs detection by Gamma probe; a dual tracers (isotope and blue dye) was performed to minimize the likelihood of missing SNs. The use of single tracer, blue dye, was not permitted in this study. All SN(s) were examined intra-operative by cytology imprint with 5% false negative according to our lab findings.

### *Histopathological Examination*

The various biomarkers were evaluated on the primary breast lesion and axillary lymph node before and after NACT. The pathological rapport mentioned the number of SN(s), the number non-SN(s), the presence or absence of atypical tumour cells (macro- or micro-metastases and/or isolated tumour cells) with or without extra capsular extension. The presence of isolated tumour cells was considered as positive SN. The oestrogen (ER), progesterone (PR), Ki-67 and human epithelial growth factor 2 (HER-2) receptors were determined on the breast tumour by using immunohistochemical staining. The tumour was considered hormone sensitive if more than 10% of ER and PR were present on the stained tumour cells and Allred score was 4 to 8. HER-2 receptors scoring varied between 0 and 3 and was always followed by gene amplification using fluorescence in situ hybridization (FISH) technique. HER-2 was considered positive if the FISH test was positive.

### *Adjuvant Therapy*

The patients who had breast conservative surgery also received whole breast irradiation and a boost. In case of positive lymph nodes also axillary radiotherapy was given. Patients who underwent a mastectomy received radiotherapy depending on axillary state. Subsequent systemic therapies were determined based on tumour response on NACT and the tumour characteristics. For breast tumours expressing hormone receptors, tamoxifen or aromatase inhibitors (plus luteinizing hormone-releasing hormone analogues in premenopausal patients) were prescribed for at least 5 years. In case of HER-2 overexpressing, Trastuzumab was given during paclitaxel (3 months) and post-operative for 9 months.

### *Outcomes*

The goal of this study was to determine the negative predictive value (NPV) and False omission rate (FOR) of the SN procedure after NACT, regardless the clinical node-stage before NACT. A secondary endpoint was to determine if ALND could be avoided after NACT in case of cN0 before NACT or after 6 weeks of treatment with normalisation of  $^{18}\text{F}$ -FDG PET-CT imaging and intra-operative negative sentinel node.

### *Statistical Analysis*

All data were collected and encoded into a Microsoft Excel Program and analysed using Fischer's exact test. 150 patients were recruited in our study of which 129 patients were eligible for analysis. Multivariate analysis was conducted on the study group. NPV and FOR were calculated on SNB after NACT regardless the primary clinical staging of the axillary lymph nodes. Sub-analysis of primarily clinical negative SN of 45 patients (34.8%) and clinical negative SN after 6 weeks NACT of 22 patients (17%), by normalization of  $^{18}\text{F}$ -FDG PET-CT scan, was also performed.

## Results

This population study consisted of 129 female patients with an invasive breast cancer. All patients received NACT and had a SN followed by ALND without taking in consideration the intraoperative result of SN. The TNM classification of patients was cT2-3N0-3M0 or cT1N1-3M0. The pathological state of the SN and ALND are given in table 1. The SN was negative in 76 (59%) patients and in 6 patients the ALND was positive (false negative). A positive SN was found in 53 (41%) patients and 21 of them had a negative ALND (false positive). The positive predictive value was 60% while negative predictive value was 92%. The sensitivity and specificity of SN procedure was 84% and 76% respectively. The FOR was calculated by  $1 - \text{NPV}$  which equals 8%. These results were calculated without taking in consideration other variables such as tumour size, pathological type and clinical axillary state. Out of the 129 patients, there were 45 patients (34.9%) who had clinical negative node (cN0) before NACT. Two out of 45 patients had a positive SN: in one patient, the ALND was negative and in the other the ALND was positive (Table 2). The NPV in this population group with cN0 was 95.5% and the FOR was 4.5%.

Eighty four (65.1%) patients had a cN1-3 before starting NACT. The axillary states was re-evaluated after 6 weeks of NACT by  $^{18}\text{F}$ -FDG PET-CT scan with or without axillary ultrasound. Follow up of this group revealed the absence of tumour in 22 patients (26%). Seventeen (77%) of them had a negative SN and negative ALND (ypN0) while 5 patients had positive SN (ypN1-2). From the 5 patients with a positive SN, 3 patients had a negative ALND and 2 patients had a positive ALND (Table 3). The NPV in this population with a negative SN (17 patients) was 100% and FOR 0%. The group of patients with cN0 after NACT, originally node-negative and node-positive cN1-3 who become cN0, consisted of 62 patients. The NPV in this group was 96.7% ( $43 + 17 / 45 + 17 = 96.7\%$ ).

## Discussion

Several studies have reported false negative rates of more than 10% for SN in node-positive breast cancer patients who become cN0 after NACT (15-18). A false negative rate of more than 10 % is the reason for not performing SN after NACT. Substituting a routine ALND for a SN would however have a major impact on the morbidity, particular in this group of pre-treated patients. In order to challenge this concept, we examined a consecutive series of patients with breast cancer cT1N1-3/cT2-3N0-3 who underwent NACT followed by SN and ALND. The false negative rate of SN after NACT in our group was 8%. This is lower than pre-specified threshold of 10%. After a median follow-up of almost 6 years the local and distant recurrence rate haven't changed. This provides evidence that SN after NACT is a safe and effective alternative to routine ALND for axillary staging.

The success rates and false negative rates of a SN in patients with cN0 breast cancers before the start of NACT, are like those in the adjuvant therapy. Therefore, SN in originally cN0 tumours after NACT has been incorporated in the staging of axillary state (19,20). In the current study the SN NPV of cN0 before NACT was 95.5%. In the group of patients who are cN0 before and after NACT the SN NPV is 96.7%. The differences between the two groups is small and statistically not significant.

Tumour response evaluation after NACT can be used to tailor the axillary surgery. In case of a negative SN, no ALND should be performed. The latter will lead to a reduction in postoperative morbidity, a reduction in hospitalization costs and an improved quality of life (21,22). NACT for breast cancer was originally used in locally advanced disease in order to achieve surgical resection (9). Thereafter, the indication of NACT was extended to operable diseases to down staging tumours and facilitate breast-conserving surgery (9,23). Primary systemic therapy could totally eradicate metastatic involved axillary node(s) and achieve pathological complete response (pCR) (24). In a SN FNAC study, which examined the false negative rate of SN after NACT 153 patients with a biopsy-proven node positive breast cancer, the false negative rate was 8.4 % (17). In our study the false negative rate of a negative SN in patients that achieved cN0 after NACT was 0%. The figure is much lower but a limitation is the small number of patients included in our group.

Recent studies including ACOSOG Z1071 trial showed improvement of the accuracy of SN in clinically positive node(s) by performing targeted axillary dissection (TAD). The latter is a procedure that involves the removal of the SN and the clipped positive node before the starting of NACT. The TAD procedure could decrease the false negative rate by precisely identification of all disease nodes. However, there is no consensus how we could best identify the clipped node(s) intraoperative (24,25).

The sentinel node procedure in carefully selected patient is safe 6 year after NACT. Long term follow-up is needed regarding the axillary recurrence rate, disease free survival, overall survival, prediction of pathologic complete response with <sup>18</sup>F-FDG PET-CT and prediction of pathologic complete response with MRI.

## **Conclusion**

In our prospective study, all the patients underwent SN and ALND irrespective of the clinical axillary stage before NACT and the pathological response after NACT. We concluded that SN in clinical node-negative cT2-3N0 or T1N1-3 prior to NACT has the same success rates without NACT. In mean time, our findings suggest that SN in clinical node-positive cT1N1 is feasible in patients who reach clinically complete axillary response by NACT. The ability to identify patients with an axillary complete pathological response after NACT offers the possibility of sparing additional morbidity by ALND in this population group. We believe that performing a SN in cN0 after NACT will be recommended in the future as a standard procedure. Further studies with large population group are needed to enforce our findings.

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## Tables

Table 1: The pathological state of the SN

	Axillary LN +	Axillary LN -	Total	
SNB +	32 (True positive)	21 (False positive)	53	PPV $TP/(TP+FP)$ = $32/(32+21)$ = 60%
SNB -	6 (False negative)	70 (True negative)	76	NPV= $TN/(FN+TN)$ = $70/(70+6)$ = 92%
Total	37	91	129	
	Sensitivity = $TP/(TP + FN)$ = $32/(32+6)$ = 84%	Specificity = $TN/(FP + TN)$ = $70/(70 + 21)$ = 76%		

FOR (False omission rate) =  $1 - NPV = 8\%$

Table 2: The clinical stage of the LNs before starting NACT

	cN0	cN1	cN2	cN3	total
SNB-/OC-	43	18	5	4	70
SNB+/OC-	1	16	3	1	21
SNB+/OC+	1	14	12	5	32
SNB-/OC+	0	1	3	2	6
total	45	49	23	12	129

$NPV \text{ in } N0 \text{ stage} = TN / (TN + FN)$

$NPV = 43 / (43 + 2) = 95.5\%$

$FOR = 1 - 95.5\% = 4.5\%$

Table 3: The clinical stage after 6 weeks NACT

	cN1/N0	cN2/N0	cN3/N0	total
SNB-/OC-	18/12	5/4	4/1	17
SNB+/OC-	16/2	3/1	1/0	3
SNB+/OC+	14/1	12/1	5/0	2
SNB-/OC+	1/0	3/0	2/0	0
total				22

NPV after 6 weeks neoadjuvant chemotherapy=  $TN / (TN+FN)$

NPV=  $17/17+0= 100\%$

FOR=  $1-NPV= 0\%$