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Towards rational axillary treatment in relation to neoadjuvant therapy in breast cancer ☆

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ABSTRACT

Aims: The purpose of this study is to analyse nodal staging and axillary response in breast cancer patients treated with neoadjuvant chemotherapy (NAC) to explore venues to safely spare patients axillary clearance whenever it could be avoided.
Methods: In 327 patients we determined the nodal status before NAC by ultrasound-guided cytology and if indicated by sentinel node biopsy (SNB). In patients with proven metastasis we analysed the axillary response after NAC.
Results: Before NAC, the ultrasound-guided cytology was positive in 252 patients. In the remaining 75 patients SNB was performed prior to NAC. The SNB was negative in 53 patients, thus in these patients axillary clearance could be avoided. All 274 patients with proven axillary metastases at diagnosis underwent axillary clearance after NAC. Twenty percent of the cytology-positive patients (50/252) had an axillary pathological complete remission (pCR) and 68% of the SNB-positive patients (15/22) had no lymph node (LN) metastasis after NAC. Subgroups with a high axillary pCR rate were patients with triple-negative tumours (57%) and human epidermal growth-factor receptor 2 (HER2)-positive tumours (68%) who had a pCR of the primary tumour.
Conclusions: Twenty percent of the patients with proven metastasis by cytology prior to NAC have an axillary pCR. The axillary pCR rate is very high in certain subgroups. Identification of these patients, could result in more axilla-conserving therapies.

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1. Introduction

Neoadjuvant chemotherapy (NAC) has gained widespread acceptance in patients with large operable breast cancer or lymph node (LN) metastases and is considered the standard treatment in advanced breast cancer. The rationale of axillary staging in the setting of neoadjuvant chemotherapy is twofold. Both the nodal status before neoadjuvant chemotherapy and the axillary response after neoadjuvant chemotherapy yield prognostic information. Kilbride and colleagues have suggested that nodal stage prior to neoadjuvant chemotherapy provides important prognostic information regarding the risk of treatment failure.[1] Rouzier and colleagues showed that after neoadjuvant chemotherapy, a complete remission of nodal metastases was a strong predictor of disease-free survival (48.7% versus 73.5% after 5 years).[2]

A widely accepted method to assess the initial nodal status is to perform ultrasonography of the axilla. If this reveals suspect lymph nodes, an ultrasound-guided fine-needle aspiration (FNA) can be performed to identify patients with proven metastases and those with FNA-negative lymph nodes. In the latter group and in patients without suspect lymph nodes at ultrasonography, a sentinel node biopsy (SNB) procedure can be performed. Whether to perform this nodal staging by SNB prior to, or after neoadjuvant therapy, is still a matter of debate. In a meta-analysis done by Xing et al. the identification rate and sensitivity of the SNB, performed after neoadjuvant chemotherapy, were 90% (range 72–100%) and 88% (range 67–100%).[3] They suggested that it is appropriate to perform a SNB after neoadjuvant chemotherapy. However, the accuracy of the SNB after neoadjuvant chemotherapy remains questionable due to the wide ranges in the reported sensitivity.[4] By performing a SNB before neoadjuvant chemotherapy, an accurate initial nodal stage can be obtained and patients with negative sentinel nodes (pN0sn) can be spared an axillary lymph node dissection (ALND) after neoadjuvant chemotherapy. By performing a SNB after neoadjuvant chemotherapy, an ALND will be avoided in the same group of patients, but also in patients with an axillary complete response to neoadjuvant chemotherapy. It is unsure whether patients with an axillary response in the sentinel node may be adequately treated without any regional treatment of the other locoregional lymph nodes. Furthermore, the initial nodal status will remain unknown.

Besides the timing of the SNB procedure in clinically negative patients, another interesting aspect is the response monitoring of axillary metastases in patients with proven metastasis. Physical examination and conventional imaging techniques, such as MRI and ultrasound, do not have the ability to evaluate the response of axillary lymph node metastasis.[5] At present, the most accurate assessment of the axillary tumour response is an ALND. Unfortunately, morbidity due to lymph oedema and decreased shoulder function is commonly seen after ALND. Patients who achieve a complete remission of their lymph node metastasis could potentially be treated with radiation therapy only. However, to date it is not possible to identify these patients. Therefore 'axilla-conserving therapy' is not yet among the benefits of neoadjuvant chemotherapy.

In this study we analysed patterns of axillary nodal disease in patients with breast cancer who received neoadjuvant chemotherapy. The aim of this study was to explore venues to safely spare patients axillary clearance whenever it could be avoided.

2. Patients and methods

2.1. Patients

We retrospectively analysed 327 patients with invasive breast cancer treated with neoadjuvant chemotherapy between 2000 and 2007. Indications for neoadjuvant chemotherapy were invasive breast cancer greater than 3 cm and/or at least one tumour-positive axillary lymph node and no evidence of distant metastases. All breast cancers were diagnosed by fine-needle aspiration and core biopsy was obtained to determine hormone receptors and human epidermal growth-factor receptor 2 (HER2) status and to obtain material for expression microarray analysis.[6] Axillary staging was done with ultrasonography. Patients with suspect lymph nodes underwent fine-needle aspiration. In patients with negative lymph nodes (ultrasound and/or cytology negative) a sentinel node biopsy procedure was performed prior to neoadjuvant chemotherapy.

2.2. Treatment

Patients were either participating in one of two randomised trials in the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital (NKI-AVL) in which anthracycline- and taxane-based regimens were compared or were treated off protocol with doxorubicin and cyclophosphamide (AC). The studies were approved by the Institutional Review Board. Between 2000 and 2005 patients were randomised between six cycles of AC and six cycles of doxorubicin and docetaxel (AD). Since 2005, a change of regimen based on response evaluation was introduced and HER2-positive patients were treated with a trastuzumab-based regimen. HER2-negative patients started with either three cycles of dose dense (dd) AC or three cycles of capecitabine and docetaxel (CD). After three cycles the tumour response was evaluated by contrast-enhanced MRI and patients with an unfavourable response on MRI switched to a presumably non-cross-resistant regimen (ddAC → CD or CD → ddAC). HER2-positive patients were treated with three 8-week cycles of paclitaxel, carboplatin and trastuzumab (PTC). Outside the context of these two studies some other regimens were used (Table 1).

Neoadjuvant chemotherapy was followed by breast-conserving surgery or mastectomy except for 3 patients. These patients only received radiation therapy to the breast because of occult primary breast tumours. All patients with proven axillary lymph node metastases prior to neoadjuvant chemotherapy underwent an ALND at levels I and II with level III sampling after neoadjuvant chemotherapy. Patients undergoing breast-conserving surgery received radiation to the breast. The indication for locoregional radiation therapy (chest wall and regional nodal basins) was based on the original staging before neoadjuvant chemotherapy. Hormone receptor-positive patients received adjuvant endocrine treatment for at

Table 1 – Patient and tumour characteristics at baseline.

	No.	%
Total no. of patients	327	
Age, years (mean)	47	
Range	(19–77)	
Menopausal status		
Premenopausal	220	67
Postmenopausal	91	28
Missing	16	5
Clinical tumour category		
cT0	3	1
cT1	21	6
cT2	174	53
cT3	90	28
cT4	39	12
Clinical nodal category		
cN0	106	33
cN1	213	65
cN3	8	2
Histology		
Ductal	266	81
Lobular/mixed	36/8	13
Not specified	16	5
Mucineus	1	0.3
Subtype according to receptor status		
ER-positive	168	52
Triple-negative (ER–/PR–/HER2–)	79	24
HER2-positive	80	24
Neoadjuvant chemotherapy		
(dd)AC	172	53
CD	15	4
Antracyline and taxane	51	16
PTC	41	12
Others	48	15
Surgery breast		
No surgery	3	1
Mastectomy	173	53
Breast-conserving surgery	151	46

ER: oestrogen receptor, PR: progesterone receptor; HER2: human epidermal growth-factor receptor, ddAC: dose dense doxorubicin and cyclophosphamide, CD: capecitabine and docetaxel; PTC: paclitaxel, carboplatin and trastuzumab.

least 5 years and HER2-positive patients received trastuzumab for 1 year.

2.3. *Pathological assessment*

Oestrogen receptor (ER) status and progesterone receptor (PR) status were determined by immunohistochemistry and interpreted as positive if more than 10% of the nuclei stained. HER2 status was assessed by scoring the intensity of membrane staining using immunohistochemistry. Tumours with a score of 3+ (strong homogeneous staining) were considered HER2 positive. In case of 2+ scores (moderate homogeneous staining) chromogenic *in situ* hybridisation (CISH) was used to determine amplification. Amplification was defined as a gene copy number of over five per cell. Tumours were classified in three subgroups according to their receptor status; (1) ER-positive tumours; ER-positive and HER2-negative tumours, (2) triple-negative tumours; ER-negative, PR-negative and HER2-negative tumours and (3) HER2-postive tumours.

Lymph nodes in the axillary dissection specimen were evaluated by microscopy of one cross section per lymph node after staining with haematoxylin and CAM5.2, an antibody-detecting cytokeratin 8/18 as expressed by tumour cells of almost all types of breast cancers. The primary tumour was sectioned in 5-mm thick slices and processed using haematoxylin. Immunohistochemistry was only used in lobular carcinomas or when the presence of residual tumour cells was unclear. The axillary pathological response was considered complete if no invasive tumour cells were found in the lymph nodes, while prior to neoadjuvant chemotherapy axillary lymph node metastasis had been proven and left *in situ* (thus excluding SNB-positive patients who have no axillary residual disease after neoadjuvant therapy). Pathological complete remission (pCR) of the breast was defined as no evidence of

invasive carcinoma. The finding of only carcinoma *in situ* was considered as pCR.[7]

2.4. Statistical analysis

The primary end-point used for statistical analysis was axillary pCR. A multivariate logistic regression model was built to examine the associations between pCR and tumour stage (stages 1–2 versus stages 3–4), tumour receptor status (ER-positive/HER2-negative versus HER2-positive versus triple-negative), histology (ductal versus lobular versus others) and the response to prior treatment (complete remission of the primary tumour – yes or no). The pair-wise differences in (overall and disease-free) survival between patients who were initially patients with a negative SNB before NAC (pN0(sn)), patients with an axillary complete remission and patients with residual axillary disease were tested using log-rank tests and survival curves produced using the Kaplan–Meier technique. Survival duration was calculated as time from diagnosis, and maximum duration was set at 5 years, with patients with better survival being truncated and censored at this point. Differences in clinical data were tested using the χ^2 or Fisher's exact where appropriate. The level of significance was set at 0.050.

3. Results

A total of 327 patients were included in this study. Patient and tumour characteristics are outlined in Table 1. The mean age of the patients was 47 (range 19–77) years and 220 patients were premenopausal. Most patients had stage T2 ($n = 174$), ductal tumours ($n = 266$) and were treated with (dd) AC ($n = 174$). ER-positive (HER2-negative), triple-negative (ER/PR/HER2: negative) and HER2-positive tumours were present in 168, 79 and 80 patients, respectively. After neoadjuvant chemotherapy, 151 patients were treated with breast-conserving surgery and mastectomy was performed in 173 patients.

3.1. Nodal staging prior to neoadjuvant chemotherapy

The pathological nodal status prior to neoadjuvant chemotherapy was determined by ultrasound-guided FNA. In 75 ultrasound- or cytology-negative patients a SNB procedure was performed. Based on this staging method three categories were defined (Table 2). Firstly, a group of patients with negative sentinel nodes consisting of 53 of the 75 patients in whom a sentinel biopsy was performed prior to neoadjuvant chemotherapy. Secondly patients with proven axillary metastasis by sentinel node biopsy ($n = 22$) and thirdly, patients with proven axillary metastasis by cytology ($n = 252$).

3.2. Assessment of axillary response after neoadjuvant chemotherapy

An ALND was omitted in all patients with negative sentinel nodes prior to neoadjuvant chemotherapy (pN0(sn) group). In all patients with proven axillary metastasis, an ALND was performed after neoadjuvant chemotherapy ($n = 274$). After neoadjuvant chemotherapy 65 of these 274 patients (24%) had no further nodal involvement. In the 22 patients with a positive sentinel node prior to neoadjuvant chemotherapy, 15 patients (68%) had no residual axillary disease after neoadjuvant chemotherapy. However, in these patients it remains questionable whether tumour-positive lymph nodes were present before the start of neoadjuvant chemotherapy. In 6/15 patients, pathological assessment of the lymph nodes showed signs suggestive for axillary nodal regression. This may not be the absolute evidence of previous metastatic involvement. Therefore, the axillary pCR was calculated from the patient group, in whom the positive lymph nodes were left *in situ*, thus leaving out these patients. An axillary pCR was seen in 50 of the remaining 252 patients (20%, 95% confidence interval (CI) 0.15–0.25). Of these 50 patients, 24 patients had a pCR of both the primary breast tumour and the axilla (48%). In patients with a positive sentinel node only 20% of the patients without residual axillary disease had a pCR of the primary tumour. This lower pCR rate of the primary tumour in the sentinel node group (20% versus 48%) suggests that in some of the patients with residual disease in the breast, the axillary lymph nodes left *in situ* were tumour free before the start of neoadjuvant chemotherapy and did not have a complete response to chemotherapy.

Additionally, we assessed variables that were predictive for an axillary pCR within the group of patients with proven metastasis by cytology prior to neoadjuvant chemotherapy. Multivariate analysis identified two predictors of axillary pCR: subtype according to receptor status and response of the primary breast tumour (Table 3). Among 132 ER+/HER2- negative patients, 6 achieved an axillary pCR (4%, 95% CI 0.01–0.08). Of 54 triple-negative patients, 18 patients achieved an axillary pCR (33%, 95% CI 0.22–0.48). In the HER2+ subgroup, 24 of the 63 patients achieved an axillary pCR (38%, 95% CI 0.22–0.52). Within the triple-negative and HER2+ subgroup, pCR of the primary breast tumour significantly affected the axillary pCR rate, with 8 of the 14 patients (57%, 95% CI 0.27–0.87) and 15 of the 22 patients (68%, 95% CI 0.47–0.89) achieving an axillary pCR, respectively (Table 4).

3.3. Survival according to nodal staging

Fig. 1 shows the survival of the different nodal staging groups; (1) patients who were pN0(sn) prior to neoadjuvant chemotherapy, (2) patients with an axillary pCR and (3) patients with residual lymph node metastasis. The median follow-up was 31 months (range 4–101). The overall survival and disease-free survival were significantly different between pN0(sn) patients and those with an axillary pCR ($P = 0.010$ and $P = 0.001$, respectively) and between pN0(sn) patients and patients with residual axillary disease ($P = 0.020$ and $P = 0.002$, respectively). The survival difference between patients with an axillary complete remission and patients with residual disease did not reach statistical significance.

4. Discussion

In this study we analysed 327 patients with tumours larger than 3 cm and/or lymph node metastasis, who were treated with neoadjuvant chemotherapy. We were specifically interested in the nodal status of these patients and in characteris-

Table 2 – Axillary response in different patient groups based on nodal staging prior to neoadjuvant chemotherapy.

N stage prior to NAC	pN1		pN0 (sn)	Total
	FNA +ve	SNB +ve	SNB –ve	
No. of patients	252	22	53	327
ALND done	252	22	–	274
Median LN retrieved (range)	16 (1–40)	15 (7–37)		
Patients with tumour-negative LNs	50 (20%)	15 (68%)		65
Patients with tumour-positive LN	202	7		209
1–3	102 (40%)	4 (18%)		106
>3	100 (40%)	3 (14%)		103
Correlation * pCR breast/pCR axilla	24/50 (48%)	3/15 (20%)	–	

This table shows the nodal involvement after neoadjuvant chemotherapy (NAC) in patients with a different nodal status before NAC. Patients who were initially node negative (pN0sn) were spared axillary clearance.

Abbreviations: NAC: neoadjuvant chemotherapy; pN: pathological nodal status determined by either Fine Needle Aspiration (FNA) or sentinel node procedure (SNB); pN0(sn): patients with a negative SNB before NAC, ALND: axillary lymph node dissection; LN: lymph node; pCR: pathological complete remission.

* No. of patients without residual axillary disease who also achieved a pCR of the breast.

Table 3 – Multivariate analysis of variables affecting axillary pCR rate.

		Odds ratio	95% CI	*P*-value
Subtype	HER2+ versus ER+	8.4	3.0–23.3	<0.001
	Triple-negative versus ER+	8.6	3.0–24.6	
pCR primary tumour	Yes versus no	7.4	3.2–17.1	<0.001
cT stage	cT1–2 versus cT3–4	1.3	0.6–2.8	NS
Histology	Lobular versus ductal	1.2	0.3–4.8	NS

ER: oestrogen receptor, HER2: human epidermal growth-factor receptor 2; pCR: pathological complete remission; 95% CI: 95% confidence interval.

Table 4 – The association between remission of axillary lymph node metastases and remission of the primary tumour in the breast within different subtypes of breast cancers.

	Axillary pCR no. (% within group)	*P*-value
ER+/HER2– ($n = 132$)	6 (4)	0.066
pCR breast ($n = 9$)	2 (20)	
No. of pCR breast ($n = 123$)	4 (3)	
Triple-negative ($n = 54$)	18 (33)	0.047
pCR breast ($n = 14$)	8 (57)	
No. of pCR breast ($n = 39$)	10 (25)	
HER2: + ($n = 63$)	24 (38)	0.001
pCR breast ($n = 22$)	15 (68)	
No. of pCR breast ($n = 42$)	9 (22)	

Within the subtypes based on hormone receptor, axillary pCR is significantly associated with pCR of the breast. pCR: pathological complete remission, ER: oestrogen receptor, HER2: human epidermal growth-factor receptor 2.

tics of patients who achieved an axillary pCR. The determination of the nodal status is performed either before or after neoadjuvant chemotherapy. We have chosen to do it prior to chemotherapy, since we expected initial nodal status to have implications for prognosis and treatment selection.

To assess the initial nodal status we started with ultrasound-guided FNA. In patients without suspect lymph nodes upon ultrasonography as well as in FNA-negative patients, a SNB procedure prior to neoadjuvant chemotherapy was performed. In the majority (71%) of these patients, the sentinel node was negative and they could thus be spared an ALND. The alternative would have been to perform the SNB procedure after neoadjuvant chemotherapy. The advantages of such an approach would be that only a single surgical procedure is required and patients with an axillary response might be spared an ALND. However, it is difficult to distinguish between patients who are initially node negative and patients who have initially axillary metastasis and a complete response. In the latter group it might be questionable if the patients are treated sufficiently without both surgery and

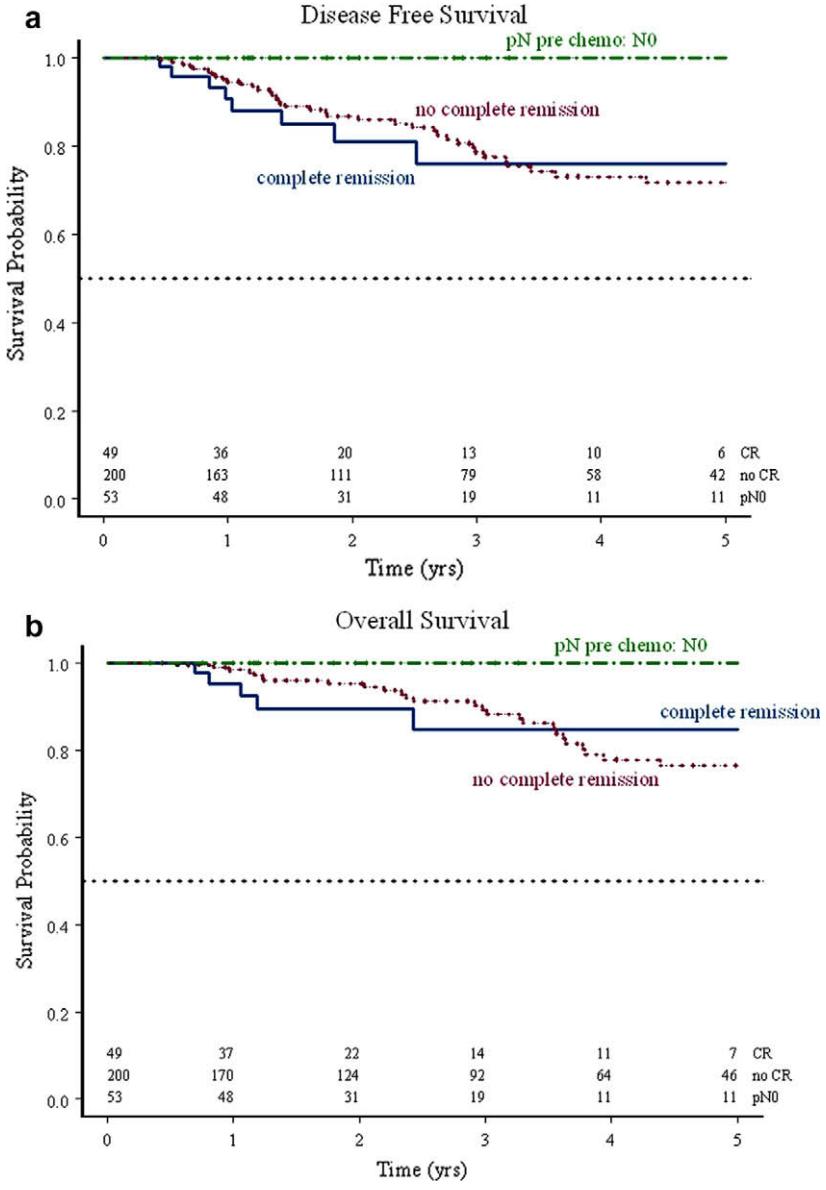

Fig. 1 – Survival according to nodal status after neoadjuvant chemotherapy. The patients are categorised in three subgroups according to their nodal status: (1) patients who were pN0 before NAC (*green*), (2) patients with nodal metastasis before NAC who obtained an axillary pCR independent of the response of the tumour (*blue*) and (3) patients with residual axillary disease (*purple*) Patients who were pN0 at diagnosis had a significant disease-free survival benefit (a, $P = 0.001$) and survival benefit (b, $P = 0.010$) compared to patients with axillary pCR. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

axillary radiation therapy. Currently, no long follow-up data are known to prove the safety of this approach. Furthermore the initially N1 status might influence treatment planning of locoregional radiotherapy. Therefore, it is important to have knowledge regarding the presence metastases, especially macrometastases, before the administration of chemotherapy. With the introduction of fluor-18-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT, the detection of nodal macrometastases that are missed by ultrasound examination, has increased.[8,9] It could be argued that patients with an ultrasonographically and FDG-PET/CT-negative axilla might be treated with a sentinel node biopsy after neoadjuvant chemotherapy, since the majority of the patients with initially evident macrometastases will be diagnosed by either one of the two techniques.

In our series, 20% of the patients with proven metastasis prior to neoadjuvant chemotherapy achieved an axillary pCR. It is important to reliably identify these patients in order to treat the axilla more conservatively. Our results suggest that there are subgroups of patients in which an 'axilla conserving' approach could be discussed because of a high axillary pCR rate. Patients with triple-negative tumours and patients with HER2-positive tumours show a high axillary pCR rate. It is critical to note that the majority of HER2-posi-

tive tumours are treated with trastuzumab. Moreover, in patients achieving a pCR of the primary tumour, the axillary pCR rate was 57% and 68%, respectively. On the contrary, patients with ER-positive tumours rarely achieve an axillary pCR, 4%. These results suggest that an ALND will remain indicated in ER-positive patients. In patients with triple-negative tumours and HER2-positive tumours it is very important to detect the large group of patients with an axillary complete remission to enable axilla-conserving treatment in this specific group.

A method to assess axillary tumour response in patients with initially proven lymph node metastasis is to perform a SNB procedure after the completion of neoadjuvant chemotherapy. We were therefore specifically interested in the accuracy of the SNB procedure in patients with *proven* metastases. We systematically reviewed all studies reporting the sentinel node biopsy results after neoadjuvant chemotherapy in N1 patients (Table 5). Nineteen studies were identified which included a total of 793 patients. The pooled identification rate was 85% (range 68–100%) and the pooled sensitivity was 89% (67–100%).[10–28] The low identification rate may be caused by chemotherapy-induced fibrosis within the axilla making accurate identification of the sentinel node more difficult. Although the sensitivity is quite high, 89%, the range is wide. Tumour presence in the lymphatic channels may obstruct flow or alter drainage patterns. Moreover, regression of metastatic disease in a non-orderly manner may cause false-negative results.[19] Remarkably, the axillary pCR rate found in the meta-analysis (35%) was high compared to the pCR rate in our study after ALND (20%) and other large studies (23%).[2,29]

Table 5 – The accuracy of the SNB procedure in patients with initially proven lymph node metastasis treated with PST.

	No. of patients cN1 prior to PST	Identification rate	No. of patients with positive SNB	False-negative rate*	Axillary pCR
Nason (2000) Cancer[19]	6	83% (5)	3	33% (1)	2/5 (40%)
Breslin (2000) JCO[10]	19	84% (16)	12	17% (2)	4/16 (25%)
Stearns (2002) Ann Surg Oncol[25]	26	88% (23)	Unknown	(3)	Unknown
Julian (2002) Am J Surg[13]	24	96% (23)	Unknown	0% (0)	Unknown
Balch (2003) Ann Surg Oncol[27]	12	100% (12)	Unknown	Unknown	Unknown
Schwartz (2003) Breast J[22]	12	100%(12)	Unknown	1	Unknown
Reitsamer (2003) J Surg Oncol[21]	13	69% (9)	Unknown	1	Unknown
Shimazu (2004) Cancer[24]	22	91% (20)	19	16% (3)	1/20 (5%)
Kang (2004) World J Surg[14]	54	72.2% (39)	27	11% (3)	12/39 (31%)
Lang (2004) Am Coll Surg[16]	23	91% (21)	11	9% (1)	10/21 (48%)
Jones (2005) Am J Surg[12]	19	68% (13)	8	13% (1)	5/13 (38%)
Mamounas (2005) JCO[18]	102	86.3% (88)	43	7.0 (3)	45/88 (50%)
Shen (2007) Cancer[23]	69	93% (64)	40	25% (10)	16/56 (29%)
Newman (2007) Ann Surg Oncol[20]	54	98% (53)	36	8% (3/36)	17/53 (32%)
Kinoshita (2007) Breast Cancer[15]	50	90% (45)	26	8.0 (2)	19/45 (42%)
Lee (2007) Breast Cancer Res Treat[17]	219	77.6% (170)	124	5.6 (7)	46/170 (27%)
Gimbergues (2008) Ann Surg Oncol[11]	47	93.7% (44)	27	29.6 (8)	17/44(39%)
Tausch (2008) Ann Surg Oncol[26]	46	Unknown	25	12% (3)	21/46 (46%)
Hino (2008) Surg Today[28]	22	77% (17)	Unknown	0% (0)	Unknown
Total weighted for *N*	793	85% (68–100)	401	11% (0–33)	35% (5–50)

cN1: positive lymph nodes by palpation or ultrasound, PST: neoadjuvant chemotherapy, SNB: sentinel node biopsy, pCR: pathological complete remission.

*False-negative rate: false-negative/true-positive + false-negative.

This raises the possibility that the pCR rate was overestimated due to inaccurate staging. Thus, the accuracy of SNB procedure to assess the axillary response to neoadjuvant chemotherapy in N1 patients remains questionable and needs further investigation.

Future goals are to develop new tools to assess the axillary response to neoadjuvant chemotherapy and to reliably select patients for axilla-conserving treatment, especially in the triple-negative and HER2-positive patients. Recently, we initiated a trial to assess the axillary response by FDG-PET/CT. We, furthermore, developed a new procedure, the MARI procedure, Mapping of the Axilla with Radioactive I-125 seeds. Positive lymph nodes are being marked with radioactive I-125 seeds prior to neoadjuvant chemotherapy and are detected afterwards to assess the axillary response.

In conclusion, the time point of the sentinel node procedure in patients with an ultrasonographically negative axilla prior to neoadjuvant chemotherapy remains questionable. By performing a sentinel node biopsy prior to neoadjuvant chemotherapy we showed that 30% of these patients have axillary metastases. In our opinion it is relevant to reveal the initial presence of lymph node metastases since it yields prognostic information and affects the radiotherapy planning. In cytologically proven N1 patients, it is desirable to identify patients with an axillary pCR to treat them more conservatively. We have shown a high axillary pCR rate in patients with triple-negative tumours and HER2-positive tumours, when a pCR of the primary breast tumour is achieved.

Conflict of interest statement

None declared.

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