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Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy – Results from the multi-center SENTINA trial

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1. Introduction

Sentinel lymph node biopsy (SLNB) is the gold standard to determine the axillary lymph node status in clinically node-negative breast cancer patients, who undergo primary surgery. To determine cN status in clinical practice palpation and ultrasound is widely used as a standard of care [1]. While mammography and/or MRI or even PET imaging can provide further information about axillary lymph nodes [2], ultrasound is regarded as the most useful technique to determine the clinical axillary nodal status. Furthermore ultrasound allows for image-guided fine-needle-aspiration (FNA)/core-needle-biopsy (CNB) in patients with suspicious nodes to confirm presence of malignant cells among cN1 patients [3]. Although the role of axillary lymph node staging is declining in breast cancer patients who undergo primary surgery, the determination of the cN status is gaining substantial interest in patients after neoadjuvant chemotherapy (NST) [4]. The assessment of patients who present initially with node positive disease and who convert to cN0 axillary status after NST is of utmost importance. The goal is a reduction of axillary surgery in patients with a good response to NST and convert to proven lymph node negative status.

Neoadjuvant systemic treatment (NST) is increasingly recognized as a tool to reduce the extent of breast cancer surgery and to develop new therapeutic concepts, that include a modification of treatment intensity according to the response to NST [5,6]. In this context, determining the postneoadjuvant cN (ycN) status is of major importance, and the role of SLNB following neoadjuvant chemotherapy is still under discussion [7,8]. Furthermore the postneoadjuvant pathological lymph node status is an important factor for the determination of a complete histopathologic remission (pCR), which is more and more considered as a prognostic factor with a high potential to tailor future locoregional treatment and postneoadjuvant treatment concepts [9]. In contrast to the adjuvant setting where even if 1–2 sentinel nodes are positive, axillary dissection (ALND) is no longer mandatory, it is unclear how to manage the axilla in the same situation after NST [10].

Especially axillary ultrasound is associated with a high intra- and interobserver variability, and trials investing the predictive value of axillary ultrasound on predicting nodal status are usually either focused on the primary surgical setting. Because of the prospective multicenter trial design of the SENTINA, we were able to investigate postneodjuvant assessment of the axilla in prospectively collected data. Furthermore we have the opportunity to provide detailed information on pathological nodal status either following SNB or axillary lymph node dissection (ALND). Because of these circumstances we aim to give a detailed picture of the impact of neoadjuvant chemotherapy on the predictive value of axillary ultrasound and palpation in predicting cN status.

2. Materials and methods

The SENTINA trial is a four arm, prospective, multi-center cohort study. 103 centers in Germany and Austria were included in the study. We enrolled patients with an indication for neoadjuvant chemotherapy (at least six cycles of an anthracycline-based chemotherapy regimen recommended by the national German guideline).

Patients were allocated to four arms by clinically examination of the nodal status (palpation ultrasound) before and after neoadjuvant chemotherapy [8]. Arm A included patients with cN0 axilla before neoadjuvant chemotherapy who underwent SNB with a histological negative result (pN0sn). No further axillary surgery after completion of chemotherapy was performed. Arm B compromises patients again with a cN0 axilla before neoadjuvant chemotherapy, but SNB revealed a positive SN (pN1sn). These patients underwent a second SNB followed by axillary lymph node dissection after completion of chemotherapy. Arm C of the study included patients with positive axillary lymph nodes before neoadjuvant chemotherapy (cN1) who converted to a clinical negative axilla during neoadjuvant chemotherapy (ycN0). After downstaging these patients underwent SNB followed by axillary lymph node dissection. Arm D compromised patients with positive axillary lymph nodes before neoadjuvant chemotherapy (cN1), who did not achieve a remission during chemotherapy (ycN1). These patients did not undergo SNB and therefore received solely axillary lymph node dissection. In this subset analysis we only included patients from arm C/D *(only these arms had an evaluation of the axilla following NST)* of the trial to asses the prediction of axillary lymph node status by palpation and ultrasound in a combined evaluation.

The clinically assessment of axillary lymph nodes included palpation and ultrasound. The classification of the clinical nodal status was performed using cN0/cN1 classification. Palpable lymph nodes in the axilla with an unsuspicious axillary ultrasound finding (based on size und normal morphologic appearance based on hilum/cortex structure) were classified as cN0. Although no uniformly accepted criteria for the ultrasound assessment of lymph nodes are available we decided to classify lymph nodes as suspicious if they demonstrated a hilum/cortex relation >2:1 or a total loss of the hilum of the node. Preoperative FNA or CNB was recommended but not mandated. SNB was only allowed in case of negative fine- or core-needle biopsy resulting in cN0 status.

The primary objective of the SENTINA trial was the accuracy of SNB in patients who presented initially as cN1 and subsequently downstaged to cN0 during neoadjuvant chemotherapy, measured by false-negative rates of the SNB [8]. Secondary endpoints were the sentinel node detection rate before and after neoadjuvant chemotherapy, as well as following SNB and neoadjuvant chemotherapy [8]. In this retrospective analysis of arm C/D we evaluated the diagnostic performance of palpation and ultrasound and compared these results with the pathologic examination on the excised nodes from ALND.

2.1. Statistical analysis

We conducted a descriptive analysis, using cross-tabulations of palpation, sonography and overall clinical evaluation of axillary lymph nodes after NST versus true histological nodal status. The false negative rates (FNR), sensitivity, specificity, false positive rates (FPR), negative predictive value (NPV) and positive predictive value (PPV) are reported with exact 95% confidence intervals (for sensitivity and specifity). The cross-tabulations of palpation, sonography and overall clinical evaluation of axillary lymph nodes after NST versus the number of histologically involved lymph nodes (sentinel

and non-sentinel) are also reported. Specifity and sensitivity are compared between palpation, ultrasound, and combined evaluation using McNemar test. In a preplanned subset analysis we stratified our results for large and small participating centers, the definition of large center was more than 50 recruited patients/center.

3. Results

3.1. Patient population

1240 breast cancer patients undergoing NST were included into the SENTINA trial. Of these 715 were classified as cN1 before NST. Of these patients 592 were classified as ycN0 after NST (arm C) and 123 remained ycN1 (arm D). Both arms demonstrated comparable baseline characteristics as shown in Table 1, with exception of lymphovascular invasion ($p = 0.001$). To evaluate the diagnostic performance of palpation and ultrasound we combined arm C and arm D patients, because all of these patients underwent ALND.

3.2. Accuracy of palpation

In case of negative palpation following NST positive nodes in ALND specimens were detected in 352 patients (53.4%), and negative nodes in 307 patients (46.6%) (see Table 2). Sensitivity of palpation in predicting cN status was 8.3% (95% C.I.: 5.8−11.6) and specificity 94.8% (95% C.I.: 91.7−96.9). The NPV was 46.6%, and the positive predictive value (PPV) was 65.3% (see Table 2).

3.3. Accuracy of ultrasound

If investigators classified ultrasound findings as cN0 following NST in 299 patients (50.3%) negative lymph nodes and in 296 patients (49.7%) positive lymph nodes were revealed by pathologic examination of the ALND specimens (see Table 3). These findings resulted in a sensitivity of axillary ultrasound following NST in 23.9% (95% C.I.: 19.8−28.5) and specificity 91.7% (95% C.I.: 88.2−94.5) (see Table 3).

3.4. Accuracy of combined evaluation

The combined evaluation included palpation and ultrasound results. If investigators classified patients as cN0 following NST in 298 patients (50.3%) negative and in 294 patients (49.7%) positive axillary lymph nodes were detected following NST (see Table 4). Respectively sensitivity was 24.4% (95% C.I.: 20.2−29.0), specificity 91.4% (95% C.I.: 87.8−94.2) (see Table 4).

3.5. Comparision between sensitivity/specifity of palpation, ultrasound, and compared evaluation

In a next step we compared sensitivity of palpation vs. ultrasound ($p < 0.001$), palpation vs. combined analysis ($p < 0.001$), and ultrasound vs. combined analysis ($p = 0.75$). We also compared specificity of palpation vs. ultrasound ($p = 0.13$), palpation vs. combined analysis ($p = 0.11$), and ultrasound vs. combined analysis ($p = 1.00$).

3.6. Accuracy after stratification for extent of axillary involvement

Another clinically important issue could be the extent of axillary involvement. We therefore stratified our results for the number of involved nodes. In case of a cN0 status defined by palpation in 181 patients (27.5%) more than two nodes were positive in ALND (see Table 5). In case of cN0 status defined by axillary ultrasound 299 (50.3%) were pN0 and 153 (25.7%) patients had one or two positive nodes. In 143 (24.0%) patients more than two positive nodes were found (see Table 5). As expected from the prior results these findings were very similar in the combined cN status. Hereby the cN0 combined evaluation status was associated with 298 (50.3%) pN0 patients, 151 (25.5%) patients with 1−2 involved nodes, and 143 (24.2%) patients with more than 2 positive nodes (see Table 5).

3.7. Accuracy after stratification for large participating centers

The combined evaluation included palpation and ultrasound results. If investigators classified patients as cN0 following NST in

Table 1
Baseline characteristics.

Parameter	Parameter value	C	D	P-value
Age, years	Mean	50	51	0.277
	Median	49	50	
	Min, Max	22, 98	29, 87	
Clinical tumor size	<=20 mm	21 (3.9)	8 (6.8)	0.071
	>20-<=50 mm	472 (87.6)	93 (79.5)	
	>50 mm	46 (8.5)	16 (13.7)	
	Missing	53	6	
Grading	G1	14 (2.9)	5 (5.1)	0.449
	G2	216 (44.3)	46 (46.5)	
	G3	258 (52.9)	48 (48.5)	
	Missing	104	24	
ER/PgR status	Both ER, PgR negative	213 (40.0)	45 (42.5)	0.655
	ER and/or PgR positive	319 (60.0)	61 (57.5)	
	Missing	60	17	
HER2 status	Negative	359 (67.5)	80 (75.5)	0.109
	Positive	173 (32.5)	26 (24.5)	
	Missing	60	17	
Lymphovascular invasion	No	372 (74.1)	62 (57.9)	0.001
	Yes	130 (25.9)	45 (42.1)	
	Missing	90	16	
Histological tumor type	Ductal invasive	476 (86.9)	91 (81.3)	0.282
	Lobular invasive	35 (6.4)	11 (9.8)	
	Other	37 (6.8)	10 (8.9)	
	Missing	44	11	

Table 2
Arm C/D pathologic nodal status vs. palpation results of cN status.

	cN after NST by palpation									
	Missing				Negative				Positive	
	N		%		N		%		N	%
pN										
Negative	2		28.6		307		46.6		17	34.7
Positive	5		71.4		352		53.4		32	65.3
Predictive test	True negative	False negative	True positive	False positive	Sensitivity, %	False negative rate, %	Specificity, %	False positive rate, %	Positive predictive value, %	Negative predictive value, %
cN after NACT by palpation	307	352	32	17	8.3	91.7	94.8	5.2	65.3	46.6

Table 3
Arm C/D pathologic nodal status vs. axillary ultrasound interpretation of cN status.

	cN after NST by ultrasound									
	Negative								Positive	
	N				%				N	%
pN										
Negative	299				50.3				27	22.5
Positive	296				49.7				93	77.5
Predictive test	True negative	False negative	True positive	False positive	Sensitivity, %	False negative rate, %	Specificity, %	False positive rate, %	Positive predictive value, %	Negative predictive value, %
cN after NACT by US	299	296	93	27	23.9	76.1	91.7	8.3	77.5	50.3

Table 4
Arm C/D pathologic nodal status vs. investigator defined cN status.

	cN after NST overall evaluation									
	Negative								Positive	
	N				%				N	%
pN										
Negative	298				50.3				28	22.8
Positive	294				49.7				95	77.2
Predictive test	True negative	False negative	True positive	False positive	Sensitivity, %	False negative rate, %	Specificity, %	False positive rate, %	Positive predictive value, %	Negative predictive value, %
cN after NACT overall evaluation	298	294	95	28	24.4	75.6	91.4	8.6	77.2	50.3

Table 5
Number of involved nodes stratified for cN status defined by papation, ultrasound, and combined investigators evaluation.

	Missing		Negative		Positive	
	N	%	N	%	N	%
cN after NST by palpation						
Number of involved nodes						
0	2	28.6	307	46.6	17	34.7
1	1	14.3	115	17.4	7	14.3
2	0	0.00	56	8.5	6	12.2
>2	4	57.1	181	27.5	19	38.8
cN after NST by ultrasound						
Number of involved nodes						
0			299	50.3	27	22.5
1			101	17.0	22	18.3
2			52	8.7	10	8.3
>2			143	24.0	61	50.8
cN after NST by investigators evaluation						
Number of involved nodes						
0			298	50.3	28	22.8
1			100	16.9	23	18.7
2			51	8.6	11	8.9
>2			143	24.2	61	49.6

143 patients (50.5%) negative and in 140 patients (49.5%) positive axillary lymph nodes were detected following NST (see Table 6). Respectively sensitivity was 25.5%, specificity 91.7%, NPV 50.5%, and PPV 78.7% (see Table 6). In large centers we do see similar results when stratifying for the extent of axillary involvement. The cN0 investigators evaluation was associated with 143 (50.5%) pN0 patients, 70 (24.7%) patients with 1–2 involved nodes, and 70 (24.7%) patients with more than 2 positive nodes (see suppl. Table 1).

4. Discussion

Evaluation of the cN0 status is crucial and well established in primary breast cancer. However the impact of NST on the assessment of the axillary status after chemotherapy is currently under investigation. Our results demonstrate that the diagnostic performance of palpation and ultrasound in predicting cN0 status is negatively influenced by NST.

In the preoperative setting the reported sensitivity and specificity derived from axillary ultrasound varies dramatically [11]. These observations might be explained by inter- and intraobserver-

Table 6
Arm C/D pathologic nodal status vs. investigator defined cN status in large centers.

	cN after NST overall evaluation									
	Negative						Positive			
	N					%	N			%
pN										
Negative	143					50.53	13			21.31
Positive	140					49.47	48			78.69
Predictive test	True negative	False negative	True positive	False positive	Sensitivity, %	False negative rate, %	Specificity, %	False positive rate, %	Positive predictive value, %	Negative predictive value, %
cN after NACT overall evaluation	143	140	48	13	25.5	74.5	91.7	8.3	78.7	50.5

variability, a well-known phenomenon in ultrasound examinations, and experience of the examiner or center effects. Just recently a retrospective case series from Memorial-Sloan-Kettering Cancer Center by Pilewskie et al. [12] demonstrated that in patients with suspicious nodes on imaging in clinically node negative patients, 71% of patients did not meet the criteria for ALND according the Z0011 data [10]. The authors therefore conclude that suspicious nodes in axillary imaging using mammography, ultrasound, or MRI are not reliable indicators for the need of ALND in T1/2 cN0 patients intended to undergo breast conservation [12]. The diagnostic performance of axillary ultrasound in predicting the axillary lymph node status might be improved by CNB or FNA [13,14]. However Pilewskie et al. [15] reported the significant association between one obvious abnormal node present on ultrasound (intended to undergo CNB or FNA) and $\geq$3 positive nodes in ALND specimens. In the SENTINA trial 25% of the patients in arm C/D underwent FNA or CNB to confirm pathologically the nodal involvement prior to NST [8]. However following NST we have no data on FNA or CNB because the study protocol mandated SNB and ALNE, therefore the investigators had no indication for an invasive procedure. We are therefore not able to answer the role of ultrasound guided FNA or CNB following NST for the prediction of axillary lymph node status.

In the post NST setting the SENTINA [8] and the Z1071 [7] trial investigated the role of SNB after downstaging of the axilla. In this clinical important setting there might be an even more important role for imaging techniques predicting axillary lymph node status. Boughey et al. [16] reported that considering cN status derived from axillary ultrasound following NST as a stratification criterium for SNB demonstrated a FNR of 9,8% in the Z1071 trial. This data suggested a role for imaging techniques in decreasing the FNR of SNB following NST. However, only 171 (43.2%) patients with an unsuspicious ultrasound finding had histologically negative lymph nodes following ALND. Although the preoperative axillary ultrasound was classified as cN0, one to three positive nodes were found in 173 (43.7%), 4–10 positive nodes in 42 (10.6%), and >10 positive nodes in 10 (2.5%) respectively. This data is very similar to the data presented from the SENTINA. Harvey et al. [17] discussed these suggesting that the FNR analysis involving the ultrasound is underpowered and point out that there was no statistical significant difference in the FNR rate [16]. But similar to Pilewskie et al. [15] there were statistically more involved nodes in case of abnormal axillary ultrasound following NST [16].

The published data on axillary ultrasound following NST is heterogenous [18]. In a systematic review published recently only 4 retrospective single center studies were eligible for further evaluation with 572 patients. The reported PPV ranged from 40 to 100%. The authors therefore conclude that there is currently no accurate non-invasive method for restaging of the axilla following NST [18]. In a recent published single center cohort the diagnostic performance of axillary ultrasound demonstrated a sensitivity of 50% and a specificity of 77%. Again a small study only including 139 patients and a retrospective single center cohort potentially influenced by PET or MRI findings [19]. The differences between the similar data in SENTINA and Z1071 [16] compared to the retrospective single-centers studies might be explained by the interobserver-variability, the experience of the centers, and a bias from other imaging techniques on pCR in breast and/or lymph nodes. However we want to point out that both prospective multi-center trials revealed very similar results on the diagnostic performance of axillary ultrasound and that we could not detect a clinically relevant difference in predicting cN status following NST in large participating centers.

Improving the diagnostic performance by wire localization of involved and marked lymph nodes allowing targeted lymph node dissection is currently under investigation [20–22]. Caudle et al. [22] demonstrated a FNR of 4.2% for targeted axillary dissection (TAD) and a FNR of 2% for SLNB and TAD following NST. However still the ultrasound detection of the clips in the nodes following NST is a clinical relevant problem and the application of radioactive seeds to the nodes is under investigation. Another approach to improve preoperative assessment could be the implementation of further information (information from other imaging techniques, intrinsic subtypes, TNM, in breast pCR, etc.) into nomograms predicting the probability of non-sentinel metastasis similar to primary breast cancer surgery [23–25].

When interpreting the data presented there are some limitations to consider. The investigators themselves evaluated and classified the axillary lymph nodes according the recommendations mentioned above. There was no central review of the ultrasound images like in the Z1071 trial [16]. This is a subset analysis only including arm C/D of the SENTINA trial. We decided for this approach because of the detailed data on ALND specimens and clear statistical design. Also a reevaluation of the FNR of SNB similar to Boughey et al. [16] is not possible due to the SENTINA design, because patients were preoperatively classified on the basis of the cN0 status following NST in arm C (cN0 following NST) and arm D (cN1 following NST).

Best to our knowledge this is the largest series recruited from a prospective multi-center trial assessing the predictive value of palpation and ultrasound for the axillary lymph node status following NST in breast cancer patients. Our results and the results from Z1071 are very similar demonstrating that the diagnostic performance of axillary ultrasound might be influenced by NST. Single-center data demonstrates that implementation of further imaging techniques like MRI or PET can improve the accuracy but data from prospective multi-center trials are not available. Improving the accuracy in predicting axillary lymph node status will need a more comprehensive approach involving information on tumor biology, response to chemotherapy and imaging information. Another option could be the use of clipping or other

ultrastaging procedures. Nevertheless our data underline the lack of prediction of axillary lymph node status by palpation and ultrasound in breast cancer following NACT demonstrating the need for surgical staging for a correct evaluation of pCR.

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Disclosure statement

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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. This study was approved by the German National ethics committee (University of Tübingen, Germany), and the local ethic committees of the participating sites. Informed consent was obtained from all individual participants included in the study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.breast.2016.11.012.

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