Axillary Staging after Neoadjuvant Chemotherapy for Initially Node-Positive Breast Carcinoma in Germany

Initial Data from the AXSANA study

Axillastaging nach neoadjuvanter Chemotherapie bei initial nodal positivem Mammakarzinom in Deutschland

Erste Daten aus der AXSANA-Studie

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Key words

breast carcinoma, neoadjuvant chemotherapy, AXSANA, targeted axillary dissection, target lymph nodes

Schlüsselwörter

Mammakarzinom, neoadjuvante Chemotherapie, AXSANA, Targeted Axillary Dissection, Target-Lymphknoten

received	15.11.2021
accepted after revision	30.6.2022

Bibliography
Geburtsh Frauenheilk 2022; 82: 932–940
DOI 10.1055/a-1889-7883
ISSN 0016-5751

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Deutsche Version unter:
https://doi.org/10.1055/a-1889-7883
Supplementary material is available under
https://doi.org/10.1055/a-1889-7883

ABSTRACT

Introduction To date, the optimal axillary staging procedure for initially node-positive breast carcinoma patients after neoadjuvant chemotherapy (NACT) has been unclear. The aim of the AXSANA study is to prospectively compare different surgical staging techniques with respect to the oncological outcome and quality of life for the patients. Little is known about current clinical practice in Germany.

Material and Methods In this paper we analyzed data from patients enrolled in the AXSANA study at German study sites from June 2020 to March 2022.

Results During the period under investigation, 1135 patients were recruited at 143 study sites. More than three suspicious lymph nodes were initially found in 22% of patients. The target lymph node (TLN) was marked in 64% of cases. This was done with clips/coils in 83% of patients, with magnetic seeds or carbon suspension in 8% each, and with a radar marker in 1% of patients. After NACT, targeted axillary dissection (TAD) or axillary lymphadenectomy (ALND) were each planned in 48% of patients, and sentinel lymph node biopsy alone (SLNB) in 2%. Clinically, the nodal status after NACT was found to be unremarkable in 65% of cases. Histological lymph node status was correctly assessed by palpation in 65% of patients and by sonography in 69% of patients.

Conclusion At the German AXSANA study sites, TAD and ALND are currently used as the most common surgical staging procedures after NACT in initially node-positive breast cancer patients. The TLN is marked with various markers prior to NACT. Given the inadequate accuracy of clinical assessment of axillary lymph node status after NACT, it should be questioned whether axillary dissection after NACT should be performed based on clinical assessment of nodal status alone.

ZUSAMMENFASSUNG

Einleitung Das optimale axilläre Stagingverfahren für initial nodal positive MammakarzinompatientInnen nach neoadjuvanter Chemotherapie (NACT) ist bislang unklar. Die AXSANA-Studie wird mit dem Ziel durchgeführt, die verschiedenen operativen Stagingtechniken hinsichtlich ihres onkologischen Outcomes und der Lebensqualität prospektiv miteinander zu vergleichen. Über die aktuelle klinische Praxis in Deutschland ist wenig bekannt.

Material und Methoden Die Daten der von Juni 2020 bis März 2022 an deutschen Studienzentren in die AXSANA-Studie aufgenommenen PatientInnen wurden analysiert.

Ergebnisse Im Untersuchungszeitraum wurden 1135 PatientInnen an 143 Studienstandorten rekrutiert. Bei 22% der PatientInnen fanden sich initial mehr als 3 suspekte Lymphknoten. In 64% der Fälle wurde der Target-Lymphknoten (TLN) markiert. Dabei erfolgte die Markierung bei 83% der PatientInnen mit Clips/Coils, bei je 8% mit magnetischen Seeds oder Kohlenstoffsuspension und bei 1% mit einem Radarmarker. Bei jeweils 48% der PatientInnen wurde nach NACT eine Targeted Axillary Dissection (TAD) oder eine axilläre Lymphonodektomie (ALND) geplant, bei 2% eine alleinige Sentinel-Lymphknoten-Biopsie (SLNB). Klinisch wurde der Nodalstatus nach NACT in 65% der Fälle als unauffällig beurteilt. Bei 65% der Frauen wurde der histologische Lymphknotenstatus durch die Palpation und bei 69% der PatientInnen durch die Sonografie korrekt erfasst.

Schlussfolgerung An den deutschen AXSANA-Studienzentren werden derzeit die TAD und die ALND als häufigste operative Stagingverfahren nach NACT bei primär nodal positiven MammakarzinompatientInnen durchgeführt, wobei die Markierung des TLN vor NACT mit verschiedenen Markern erfolgt. Aufgrund der ungenügenden Genauigkeit der klinischen Beurteilung des axillären Lymphknotenstatus nach NACT sollte kritisch hinterfragt werden, ob eine Axilladissektion nach NACT auf der Grundlage einer alleinigen klinischen Bewertung des Nodalstatus erfolgen sollte.

Introduction

In Germany, chemotherapy for breast carcinoma is indicated on the basis of tumor biology and tumor stage, and is increasingly performed as neoadjuvant therapy [1]. In this regard, the choice of axillary operation to be performed after neoadjuvant chemotherapy (NACT) depends on the initial axillary lymph node status. In women with initially unremarkable lymph node status (cN0), detection rates (DR) and false-negative rates (FNR) of sentinel lymph node biopsy (SLNB) after NACT are equivalent to the success rates in patients undergoing primary surgery (DR > 90%, FNR < 10%) [2]. Therefore, in these patients, SLNB is recom-

mended as an axillary staging procedure both in the current German S3 guideline [3] and by the Breast Committee of the Working Group for Gynecological Oncology (Arbeitsgemeinschaft Gynäkologische Onkologie e. V., AGO) [4].

In the patient group with initially clinically suspicious axillary lymph nodes (cN+), a recent meta-analysis determined a DR of only 89 % and an FNR of 17 % for SLNB [5]. Because the detectability of the sentinel lymph node (SLN) is limited and the FNR is significantly higher than the generally accepted cut-off of 10 %, SLNB is currently not recommended in Germany as the sole axillary staging method for these patients [3, 4]. If an initially suspicious axillary lymph node, the so-called target lymph node (TLN), is removed in addition to the SLN, the FNR decreases to 2–4 % [6 – 8]. The combination of SLNB and target lymph node biopsy (TLNB) is referred to as targeted axillary dissection (TAD) and was first described by Caudle et al. in 2016 [6]. TAD could avoid the more radical axillary lymphadenectomy (ALND) in up to 60 % of patients who no longer have tumor cells in their lymph nodes after NACT despite initial lymph node metastasis [9].

In order to be able to remove the TLN specifically in the context of the TAD, it must be marked prior to NACT. To this end, various markers are being investigated in clinical trials. Not all of the available markers are approved in Germany for the localization of axillary lymph nodes. The AGO has recommended TLN marking before NACT since 2016 [10], and has classified TAD as an equivalent alternative to ALND since 2019 for patients with axillary response after NACT (ycN0) [11]. If the lymph nodes remain clinically suspicious (ycN+) after NACT or if lymph node metastases are still histologically detectable despite ycN0, the AGO recommends ALND [4]. The 2021 update of the S3 guideline recommends ALND regardless of axillary response to NACT, and does not yet mention TAD as a possible option [3].

Since to date no prospective data are available on the different axillary surgical procedures (SLNB, TLNB, TAD, ALND) in terms of oncological outcome, complications, and quality of life, the AXSANA study was initiated as a prospective, international non-interventional registry study to determine the optimal surgical axillary staging procedure for patients with initially positive nodal status having undergone neoadjuvant therapy. Recruitment at German study sites started in June 2020.

To date, there are no prospective data on the axillary management of initially node-positive breast carcinoma patients after NACT in everyday clinical practice in Germany. Therefore, in this paper, as well as characterizing the patient population after 21 months of recruitment to the AXSANA study, we also describe the frequency and type of TLN marking, and present the axillary surgical procedure chosen according to the clinical and pathological assessment of nodal status after NACT at the German study sites.

Materials and Methods

AXSANA study

The AXSANA study is a prospective, international registry study (NCT04373655; axsana.eubreast.com). It was initiated by the study group EUBREAST (European Breast Cancer Research Association of Surgical Trialists). The three primary study objectives are:

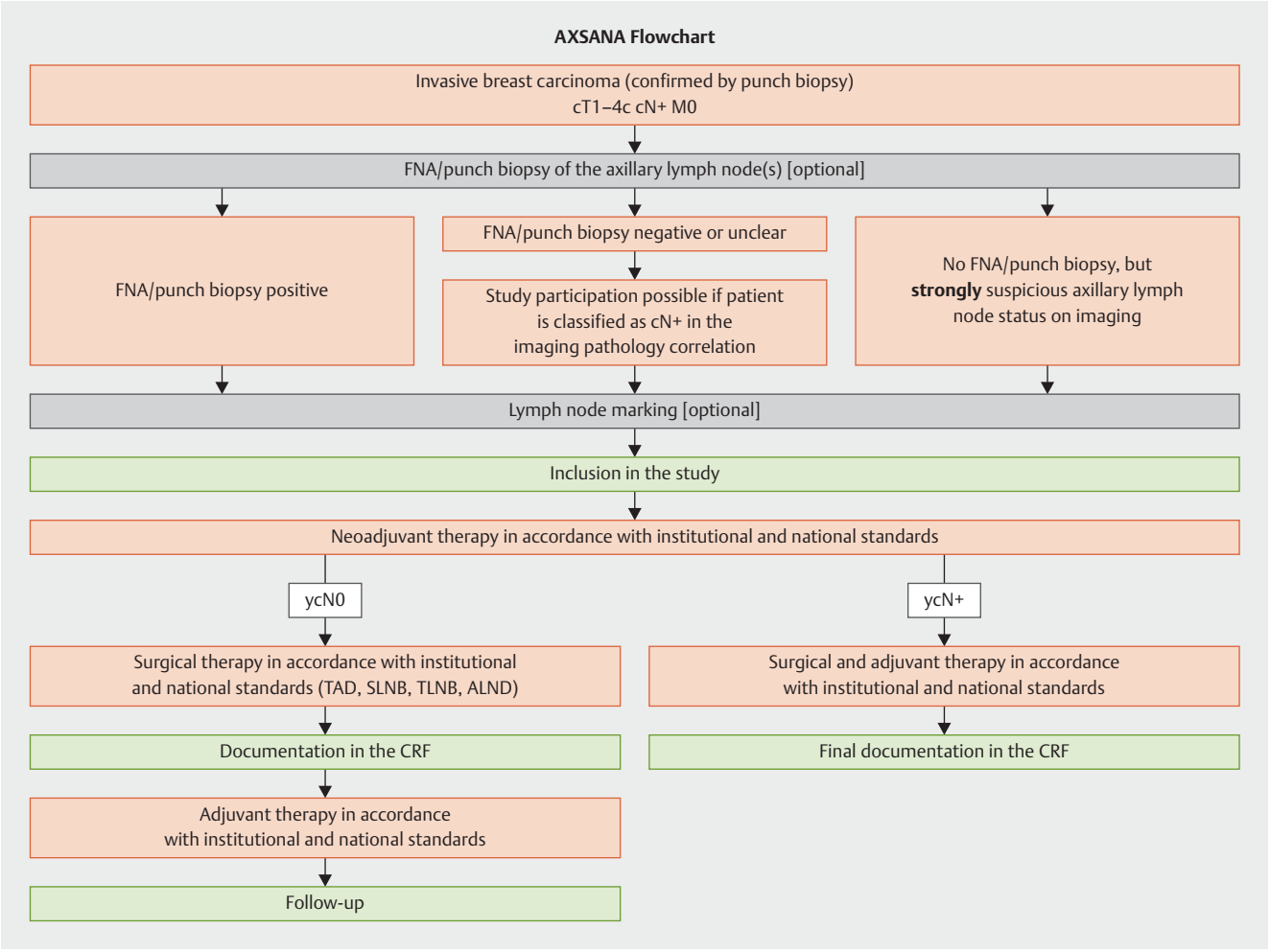
1. invasive disease-free survival,
2. axillary recurrence rate, and
3. quality of life and arm morbidity

as a function of axillary surgical technique (SLNB, TLNB, TAD, ALND) in patients with initially node-positive breast carcinoma and clinical conversion to ycN0 after NACT [12].

Since the AXSANA study is a non-interventional registry study, study participation should not influence patient therapy, which should be conducted according to institutional and national standards. TLN marking before NACT is not a requirement for study participation (▶ **Fig. 1**). All available marking and localization techniques for the TLN are allowed, and the number of TLNs marked is not limited. The inclusion and exclusion criteria for the AXSANA study are summarized in ▶ **Table 1**. The aim is to recruit a total of 3000 patients internationally across multiple study sites. Evaluation of the primary study targets is planned for 2030 [13]. Currently, 28 countries are participating in the AXSANA study. The

▶ **Table 1** Inclusion and exclusion criteria for AXSANA study according to protocol version 5.1.

Inclusion criteria	Exclusion criteria
▪ Written declaration of consent ▪ Primary invasive breast carcinoma confirmed by punch biopsy ▪ cN+ (confirmed by punch biopsy/FNA or presence of highly suspicious axillary lymph nodes on imaging) ▪ If a minimally invasive biopsy of the axillary lymph node(s) has been performed and yielded a negative or equivocal result, the patient may still participate in the study if the lymph node status is classified as cN+ in the final correlation between pathology and imaging findings. ▪ cT1–cT4 ▪ Planned neoadjuvant system therapy ▪ Female/male patients aged ≥ 18 years	▪ Distant metastatic breast carcinoma ▪ Locoregional recurrence ▪ Inflammatory breast carcinoma ▪ Extramammary breast carcinoma ▪ Bilateral breast carcinoma ▪ History of invasive breast cancer, DCIS, or a self-reported invasive malignancy ▪ Proven or suspected supraclavicular lymph node metastasis ▪ Proven or suspected parasternal lymph node metastasis ▪ Axillary operation prior to NACT (e.g., SLNB or lymph node sampling) ▪ Pregnancy at the time of admission to the study ▪ Less than 4 cycles of NACT applied ▪ Lack of operability



▶ **Fig. 1** AXSANA study design.

aim of this article is explicitly not to evaluate the primary and secondary study objectives.

Patient cohort

This paper summarized the results of all patients enrolled in the AXSANA study at German study sites from 20 June 2020 to 20 March 2022. All data were documented online by the study sites and subsequently verified via remote monitoring. Only data that were assessed as complete and plausible after remote monitoring were included in the current analysis. Because not all recruited patients had completed NACT or had undergone surgery by 20 March 2022, 665 records were available for evaluation of the questions relating to characterization of the study population and marking techniques used for the TLN before NACT (total cohort Germany), and 313 (subcohort OP+) records were available for the surgical procedure and assessment of axillary lymph node status after NACT (▶ **Fig. 2**).

Statistical data analysis

Documentation by the study sites was performed in the eCRF documentation system of the AXSANA study using the REDCap software (Department of Biomedical Informatics, Vanderbilt University, Nashville, TN, USA). Statistical analysis was performed using SAS software (SAS Institute, Cary, NC, USA). For descriptive analysis aimed at characterizing the study population and TLN marking techniques, as well as evaluating axillary management after NACT depending on clinical and pathological lymph node status, absolute and relative frequencies were reported for qualitative parameters, and mean values ± standard deviation (SD) were reported for quantitative parameters. The diagnostic value of palpation and sonography with regard to axillary lymph node status after NACT was reported using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the proportion of correctly classified cases (accuracy).

Results

Characterization of patient cohort

During the study period, a total of 1763 patients were enrolled in the AXSANA study, of whom 1135 (64.4%) were enrolled in Germany (▶ **Fig. 2**) at 143 study sites (including 13 university hospi-

tals) (supplementary material, online). At 39 of these study sites, > 10 patients were recruited. Final verified data on the characteristics of the recruited German study participants were available for 665 patients. Of these, 660 (99.2%) were female, and 5 (0.8%) were male. The clinicopathological parameters for both the total German cohort and the subcohorts with (OP+, n = 313) and without (OP−, n = 352) completed surgical documentation after NACT are shown in ▶ **Table 2**. The distribution of individual characteristics in the subcohorts is largely consistent with that of the overall cohort.

Minimally invasive biopsy and marking of the TLN before NACT (total cohort in Germany before NACT)

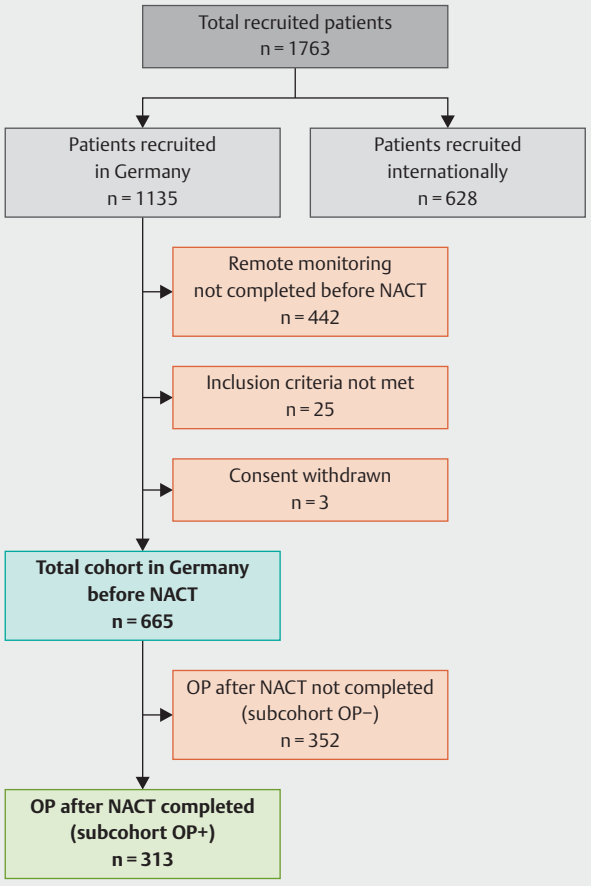
Minimally invasive biopsy of clinically suspicious lymph nodes before NACT was performed in 619 out of 665 cases (93.1%), 546 times (88.2%) in the form of a punch biopsy and 73 times (11.8%) as fine needle aspiration. In 600 cases (96.9%), this confirmed the suspicion of lymph node metastasis. However, participation in the study is possible even with negative or unclear histology/cytology but with strong imaging suspicion of the presence of lymph node metastasis, provided the lymph node status is classified as cN+ on an interdisciplinary basis. One lymph node was punctured in 581 patients (93.9%), and more than one lymph node was punctured in 38 patients (6.1%).

In 428 out of 665 cases (64.4%), suspicious axillary lymph nodes were marked before NACT. This was done 83.2% of the time with metal clips/coils (n = 356) (▶ **Table 3**), including five times (1.2%) in combination with carbon marking. Magnetic seeds were used in 8.2% of study participants (n = 35), and carbon tattoo alone in 7.7% (n = 33). A radar marker was used in four cases (0.9%); radioactive seeds and radiofrequency systems were not used. One suspicious lymph node was marked in 398 out of 428 cases (93.0%), two lymph nodes in 28 cases (6.5%), and three or more lymph nodes in two patients (0.5%). In 234 cases (54.7%), lymph node marking was only performed after the results of minimally invasive biopsy were available. The mean size of the marked lymph node was 18.6 ± 9.2 mm.

Assessment of the ypN status and planned axillary staging after NACT (OP+ subcohort)

Clinical conversion of axillary lymph node status to ycN0 (based on palpation and sonography after NACT) was documented for 203 of the 313 study participants (64.9%), whereas clinically suspicious axillary lymph nodes after NACT were still described in 109 patients (34.8%). TAD was planned in 149 cases (47.6%), and ALND in 151 cases (48.2%). An SLNB alone was planned in 7 cases (2.2%), and TLNB alone in 2 cases (0.7%). The type of operation planned depending on the clinical nodal status after NACT is listed in ▶ **Table 4**.

Among the 243 patients with an initial maximum of one to three suspicious lymph nodes, a TAD was planned in 52.3% of cases and ALND in 44.9% of cases. If more than three lymph nodes (n = 67) were initially suspicious, ALND was planned in 62.7% of study participants and TAD in 28.4%.



▶ **Fig. 2** Flowchart AXSANA enrollment status 20 March 2022 and current study cohorts.

ypN status and axillary staging after NACT (OP+ subcohort)

In 55.0% (n = 172 out of 313) of patients, axillary lymph node metastases were no longer detectable (ypN0). In 140 cases (44.7%), tumor cells were still detected histologically in the axillary lymph nodes. Micrometastases only were present in 14 out of 313 patients (4.5%), and macrometastases were present in 126 out of 313 patients (40.2%). In one case (0.3%), ypN status could not be determined because no lymph nodes were histologically detectable in the TAD preparation, and no further axillary operation was performed. If no residual tumor was detectable in the breast (n = 138), the proportion of ypN0 patients was 88.4% (n = 122). The correlation between clinical lymph node status determined by palpation and imaging and pathological lymph node status after NACT is shown in ▶ **Table 5**. A discrepancy (ycN0/ypN+ or ycN+/ypN0) was present in 97 out of 313 patients (31.0%).

For palpation to assess the status of axillary lymph nodes after NACT, sensitivity was 27.9% (95% CI 20.4–35.3%), specificity 95.4% (95% CI 92.3–98.5%), PPV 83.0% (95% CI 72.2–93.7%), NPV 62.0% (95% CI 56.2–67.9%), and accuracy 65.2% (95% CI 59.6–70.5%). A sensitivity of 52.8% (95% CI 44.1–61.6%), specificity of 81.1% (95% CI 75.1–87.2%), PPV of 68.8% (95% CI 59.5–

▶ **Table 2** Clinicopathological tumor characteristics for the subcohorts with (OP+) and without (OP−) OP data after NACT and the total cohort in Germany before NACT.

Parameters	Sub cohort OP+	Sub cohort OP−	Total cohort
Number of patients, n (%)	313 (47.1)	352 (52.9)	665 (100)
Mean age, years (± SD)	52.7 (± 11.8)	51.9 (± 11.1)	52.3 (± 11.5)
Mean BMI, kg/m² (± SD)	26.4 (± 5.5)	27.3 (± 8.6)	26.9 (± 7.3)
cT stage before NACT, n (%)			
▪ 1	80 (25.6)	97 (27.6)	177 (26.6)
▪ 2	186 (59.4)	213 (60.5)	399 (60.0)
▪ 3	35 (11.2)	37 (10.5)	72 (10.8)
▪ 4	12 (3.8)	5 (1.4)	17 (2.6)
Number of suspicious lymph nodes before NACT, n (%)			
▪ 1–3	243 (77.6)	275 (78.1)	518 (77.9)
▪ > 3	67 (21.4)	77 (21.9)	144 (21.7)
▪ No data	3 (1.0)	0 (0)	3 (0.4)
Tumor type, n (%)			
▪ Invasive ductal	290 (92.6)	317 (90.0)	607 (91.3)
▪ Invasive lobular	11 (3.5)	18 (5.1)	29 (4.4)
▪ Mixed invasive ductal/lobular	3 (1.0)	3 (0.9)	6 (0.9)
▪ Other	9 (2.9)	13 (3.7)	22 (3.3)
▪ No data	0 (0)	1 (0.3)	1 (0.1)
Grading, n (%)			
▪ 1	5 (1.6)	8 (2.3)	13 (1.9)
▪ 2	115 (36.8)	133 (37.8)	248 (37.3)
▪ 3	192 (61.3)	211 (59.9)	403 (60.6)
▪ 4	1 (0.3)	0 (0)	1 (0.2)
Tumor biology, n (%)			
▪ HR+/HER2−	135 (43.1)	174 (49.4)	309 (46.5)
▪ HR+/HER2+	71 (22.7)	74 (21.0)	145 (21.8)
▪ HR−/HER2+	48 (15.3)	40 (11.4)	88 (13.2)
▪ HR−/HER2−	59 (18.9)	64 (18.2)	123 (18.5)
Multicentricity, n (%)			
▪ Yes	58 (18.5)	54 (15.3)	112 (16.8)
▪ No	255 (81.5)	298 (84.7)	553 (83.2)

OP = operation; SD = standard deviation; BMI = body mass index; NACT = neoadjuvant chemotherapy; LN = lymph nodes; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2

78.0%), NPV of 68.6% (95% CI 62.0–75.3%), and accuracy of 68.7% (95% CI 62.9–74.0%) were determined for prediction of histological nodal status after NACT by axillary ultrasonography.

In retrospective evaluation of surgical approach depending on final histologic nodal status, ALND was performed in 50.6% (87 out of 172) of patients with ypN0 status and in 87.9% (123 out of 140 cases) of patients with ypN+ status. In 17 cases (12.9%), ALND was not performed despite ypN+, with radiation therapy to the axilla planned for 9 of these 17 patients (52.9%).

Discussion

This paper presents, for the first time, prospectively collected data on the performance of axillary staging after NACT in breast carcinoma patients with initially suspicious axillary lymph nodes in a German study population. Within the first 21 months, more than one third of the planned 3000 AXSANA study participants were recruited in Germany alone. Recruitment outside Germany started in January 2021, so reaching the planned recruitment target by the end of 2025 seems realistic [13].

The data presented here from German study participants demonstrate that ALND and TAD are the favored surgical procedures in clinical practice in Germany, in accordance with the AGO recommendation. More than one fifth of patients initially had more than three suspicious axillary lymph nodes. In the feasibility studies published to date on TAD, the total number of patients with a higher axillary tumor burden is rather low. In the SenTa study, the largest prospective multicenter study of TAD after NACT to date with 473 cases, the proportion of patients with at least three suspicious lymph nodes before NACT was 28.8% (n = 136). In these

▶ **Table 3** Markers used to mark suspicious axillary lymph nodes before NACT.

Marker	Number of patients (%)
Metal clip/coil	356 (83.2)
Of which:	
▪ Tumark Vision (Somatex)	130
▪ BIP-O-Twist-Marker (BIP Biomed. Instrumente & Produkte GmbH)	110
▪ HydroMark (Mammotome)	54
▪ Tumark Professional (Somatex)	23
▪ KliniMark Clip (KLINIKA Medical GmbH)	19
▪ UltraClipII (Bard)	5
▪ Other	15
Magnetic seed	35 (8.2)
Carbon suspension	33 (7.7)
Radar marker	4 (0.9)
Total	428 (100)

NACT = neoadjuvant chemotherapy

cases, the TLN could be successfully removed significantly less often after initial clip marking compared to the group of patients who initially had less than three suspicious lymph nodes. An FNR was not specified for this subgroup [7]. The study by Caudle et al. in which the TLN was also marked preoperatively with a radioactive iodine seed also included n = 58 (28 %) patients with at least three suspicious lymph nodes [6]. In the Dutch studies with exclusive iodine seed marking of the TLN, which is not permitted in Germany under radiation protection law, this group of patients was also allowed to participate. In Donker et al. the number was n = 41 (40 %) [14]. No data on DR or FNR in this subgroup are yet available for the RISAS study which was presented at the 2020 San Antonio Breast Cancer Symposium (SABCS) with a total of 227 cases [8]. At the German AXSANA study centers alone, 144 patients with more than three suspicious lymph nodes have already been included in the study for the evaluation period of 21 months. In these cases, ALND was planned more frequently (62.7 %) than in the group with one to three initially suspicious lymph nodes (44.9 %), while a TAD was planned in 28.4 %. Therefore, due to the high number of participants, the AXSANA study for patients with a high initial axillary tumor burden will generate much needed data on both detection and oncological safety (recurrence rates) after TAD alone.

Whether or not the clinical response of the axillary lymph nodes after NACT should be the decisive factor in the decision for or against surgical de-escalation, as recommended by the AGO [4], needs to be critically discussed on the basis of the data presented here. A discrepancy between clinical assessment and final histological lymph node status was observed in 31.0 % of patients. In nearly one in three study participants, lymph node metastases were detected histopathologically despite ycN0 status, or else there was complete axillary pathological remission despite the fact that the lymph nodes were clinically suspicious. The sensitivity of axillary ultrasonography in our collective was 52.8 %, lower than the 65 % reported in a recently published meta-analysis [15]. Sonography correctly assessed pathological lymph node sta-

▶ **Table 4** Planned axillary operation after NACT depending on ycN status (OP+ subcohort, n = 313).

Planned operation	Number of ycN+ (%)	Number of ycN0 (%)	Number with no data for ycN (%)	Total number (%)
ALND	76 (69.7)	75 (36.9)	0 (0)	151 (48.2)
SLNB	2 (1.8)	5 (2.5)	0 (0)	7 (2.2)
TLNB	1 (1.0)	1 (0.5)	0 (0)	2 (0.7)
TAD	28 (25.7)	120 (59.1)	1 (100)	149 (47.6)
Other	2 (1.8)	2 (1.0)	0 (0)	4 (1.3)
Total	109 (100.0)	203 (100.0)	1 (100)	313 (100)

ALND = axillary lymphadenectomy; SLNB = sentinel lymph node biopsy; TLNB = target lymph node biopsy; TAD = targeted axillary dissection

▶ **Table 5** Correlation between clinical and pathological lymph node status after NACT (OP+ subcohort, n = 313).

Lymph node status after NACT	Number of ypN0 (%)	Number of ypN+ (%)	Number with no data for ypN (%)	Total number (%)
ycN0	138 (68.0)	64 (31.5)	1 (0.5)	203 (100)
ycN+	33 (30.3)	76 (69.7)	0 (0)	109 (100)
No data for ycN	1 (100)	0 (0)	0 (0)	1 (100)

NACT = neoadjuvant chemotherapy; LN = lymph nodes

tus in only two thirds of study participants, and consequently performed no better than palpation. This is consistent with previously published studies [16].

For initially node-positive breast carcinoma patients, SLNB alone is not recommended by the AGO [4, 19] or in the current S3 guideline [3] as an axillary staging method after NACT due to the FNR of > 10% demonstrated in prospective, multicenter studies [17, 18]; at the German AXSANA study sites, this was only planned for 2.2% of patients. In contrast, several international guidelines recommend SLNB alone rather than TAD or ALND as the standard when more than two SLN have been removed and/or marking has been done with dye and technetium [20]. However, when planning SLNB alone, it should be kept in mind that the proportion of patients with at least three SLN detectable after NACT was only 34% in the multicenter German SENTINA study [17].

With the aim of performing TLNB or TAD after NACT, the TLN was marked in 64.4% of German AXSANA patients. In the vast majority of cases (83.4%) this was done with a metal clip. In contrast to the SenTa study, in which the Tumark Vision Clip was used 71% of the time [7], other clips were used 63.5% of the time in the AXSANA study. At the end of recruitment, accurate documentation of the clip brands used should make it possible to identify the clip with the best detectability in the axilla after NACT. Besides clip marking, magnetic seeds and carbon suspension were also used to a relevant extent. Data from several prospective studies are available for tattooing the TLN with carbon, demonstrating high detection rates of consistently greater than 90% [21]. In the largest of these studies, the multicenter TATTOO trial, a DR for the TLN of 93.6% was determined in 110 cases. The FNR was 9.1% [22], higher than in the SenTa study after clip marking (4.3%) [7] and in the RISAS study after radioactive iodine seed marking at 3.5% [8], but still within the accepted cut-off of 10%. No prospective data on TLN marking with magnetic seeds before NACT are yet available as a full-text publication. In the AXSANA study, promising radar and radio frequency-based systems (Savi Scout, LOCalizer) are also being investigated in terms of their success rates. Thus, for the first time, the AXSANA study will provide prospective and multicenter data comparing all available axillary lymph node marking techniques.

Due to the multicenter, non-interventional design of the AXSANA study, with more than 100 recruiting centers and inclusion of data verified by remote monitoring, this study was already able to generate high-quality, representative data on axillary staging after NACT in Germany just 21 months after the start of the study. The disadvantage of the study design used for this paper is that because we only evaluated monitored data sets collected at a timepoint at which the AXSANA study was not yet completed, data sets of different sizes were analyzed for each of the questions investigated. Although this allowed the examination of actual data from the largest possible number of patients for the respective questions, we must await evaluation after the end of the study in order to make definitive statements.

Conclusion

This article is the first to provide representative data on axillary staging after NACT in initially node-positive breast carcinoma patients in Germany. The evaluation shows that in routine clinical practice, TAD is the most common operation used in this cohort, along with ALND. Different techniques are used to mark and remove the TLN. The data presented here suggest that clinical assessment by palpation and sonography does not accurately predict pathological lymph node status after NACT. In a relevant proportion of patients who no longer have tumor cells in the lymph nodes after NACT, an ALND is performed unnecessarily.

Continued consistent international recruitment into the AXSANA study will provide, for the first time, a body of data based on a sufficient number of cases to compare the different surgical staging procedures in the axilla (ALND, SLNB, TAD, TLNB) in terms of oncological outcome, complication rates, and quality of life. The AGO therefore strongly recommends participation in the AXSANA study [4]. The final evaluation of the AXSANA study is planned for 2030.

Supplement

Supplement 1: The German AXSANA study group.

Acknowledgements

The authors would like to thank Angelika Jursik, Jana Shabbir, Marina Mangold and Markus Höing for the extensive and excellent coordination of the AXSANA study. Furthermore, we would like to thank all employees at the study centers who are actively involved in the AXSANA study.
The AXSANA study is supported by the AGO Breast Study Group (AGO-B), the Claudia von Schilling Foundation for Breast Cancer Research, the Ehmann Foundation Savognin, Arbeitsgemeinschaft für ästhetische, plastische und wiederherstellende Operationsverfahren in der Gynäkologie e. V. (AWOgyn), EndoMag, Merit Medical GmbH, Mammotome, German Breast Group Forschungs GmbH (GBG), and Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO e. V.).

Conflict of Interest

T. D. W. has received fees for lectures and activities from Pfizer, Roche, and NeoDynamics.
M. T. has acted in an advisory capacity for Amgen, AstraZeneca, Aurikamed, Becton & Dickinson, Biom'Up, Celgene, ClearCut, Clovis, Daiichi Sankyo, Eisai, Exact Sciences, Gilead Science, Lilly, MSD, Norgine, Neodynamics, Novartis, Onkowissen, Pfizer, pfm Medical, Pierre Fabre, Roche, RTI Surgical, Seagen, and Sysmex. He received manuscript support from Amgen, Celgene, ClearCut, pfm medical, Roche, and Servier, travel expenses from Amgen, Art Tempi, AstraZeneca, Celgene, Cleracut, Clovis, Connect Medica, Daiichi Sankyo, Eisai, Exact Sciences, Hexal, I-Med-Institute, Lilly, MCI, Medtronic, MSD, Norgine, Novartis, Omniamed, Pfizer, pfm Medical, Roche, and RTI Surgical, conference costs from Amgen, AstraZeneca, Celgene, Daiichi Sanyko, Hexal, Novartis, Pfizer, and Roche, lecturing fees from Amgen, Art Tempi, AstraZeneca, Celgene, Clovis, Connect Medica, Eisai, Genomic Health, Gilead Science, Hexal, I-Med-Institute, Jörg Eickeler, Lilly, MCI, Medtronic, MSD, Novartis, Omniamed, Pfizer, pfm Medical, Roche, RTI Surgical, Seagen, Sysmex, and Vifor, and study support from Endomag and Exact Sciences.
M. P. L. has acted in an advisory capacity for Lilly, AstraZeneca, MSD, Novartis, Pfizer, Eisai, Gilead, Exact Sciences, Daiichi Sankyo, Grünenthal, Pierre Fabre, PharmaMar, Samantree, Sysmex, and Roche. He has

given lectures for Lilly, Roche, MSD, Novartis, Pfizer, Exact Sciences, Daiichi Sankyo, Gilead, Grünenthal, AstraZeneca, pfm, Samantree, and Eisai, received travel expenses from Roche and Pfizer, and is on the Editorial Board at medac.

S. L. has received fees or research support from Abbvie, AstraZeneca, Celgene, Daiichi Sankyo, Gilead, Novartis, Pfizer, Pierre Fabre, Prime/Medscape, Roche, and Samsung. In addition, she has acted in an advisory capacity for Abbvie, Amgen, AstraZeneca, Bayer, BMS, Celgene, Daiichi Sankyo, Eirgenix, GlaxoSmithKline, Gilead, Lilly, Merck, Novaris, Pfizer, Pierre Fabre, Prime/Medscape, Puma, Roche, and Seagen, and is a member of GBG Forschungs GmbH.

H.-C. K. has received fees and travel expenses support from Carl Zeiss meditec, Theraclion, Novartis, Amgen, AstraZeneca, Pfizer, Roche, Daiichi Sankyo, Tesaro, MSD, Onkowissen, Eli Lilly, SurgVision, Exact Sciences, and Genomic Health, and holds shares in Theraclion and Phaon Scientific.

M. W. has received fees for lectures and consulting activities from Pfizer, Roche, Novartis, Lilly, GlaxoSmithKline, and AstraZeneca.

S. P. has received fees for advisory activities from Becton & Dickinson, Grünenthal, Sysmex Deutschland, Sysmex Europe, Endomag, pfm medical AG, NeoNavia, NeoDynamics, and Triconmed, as well as support for training courses from Roche and for travel activities from Motiva.

D. W. has received fees for lectures and activities from Roche and Pfizer.

M. H. has received lecture fees from Roche and Novartis.

M. U. has received fees for lectures and advisory activities from Abbvie, Amgen, AstraZeneca, BMS, Celgene, Daiji Sankyo, Eisai, Gilead, GlaxoSmithKline, Lilly, Molecular Health, MSD Merck, Mundipharma, Mylan, Myriad Genetics, Novartis, Pierre Fabre, Pfizer, Roche, Sanofi Aventis, and Saegen.

M. B.-P. receives fees for lectures and advisory activities from Roche, Novartis, Pfizer, Eli Lilly, Eisai, GlaxoSmithKline, Seagen, Daiichi Sankyo, pfm medical AG, and AstraZeneca, and study support from Exact Sciences.

The AXSANA study is financially supported by the AGO-B, the Claudia von Schilling Foundation for Breast Cancer Research, the Ehmann Foundation Savognin, AWOgyn, EndoMag, Merit Medical GmbH, and Mammotome. The sponsors of the study had no influence on the study protocol or conduct.

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