Marking Techniques for Target Lymph Nodes in Node-Positive Breast Cancer Treated With Neoadjuvant Therapy in the AXSANA/EUBREAST-03/AGO-B-053 Study

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DOI https://doi.org/10.1200/JCO-25-01921

ABSTRACT

PURPOSE Surgical axillary staging in patients with node-positive breast cancer (BC) who converted to clinical node negativity through neoadjuvant chemotherapy (NACT) has changed significantly in recent years. Targeted axillary dissection (TAD) and target lymph node (TLN) biopsy (TLNB) became increasingly popular. However, data comparing marking techniques for the TLN are limited. Here, we evaluate marking techniques in the largest prospective cohort worldwide.

MATERIALS AND METHODS Among patients from the ongoing prospective multicenter AXSANA (EUBREAST-03) study who received TLN marking and TAD/TLNB, we evaluated different marking methods with respect to detection and removal rates and clinical performance.

RESULTS Until January 6, 2025, 6,129 patients from 26 countries were enrolled. Of these patients, 2,596 had ≥1 TLN marked before NACT and completed surgery; 13.3% of the patients had ≥4 suspicious nodes at diagnosis. Pre-NACT TLN marking used a clip in 2,003 patients (77.2%), magnetic seed in 287 (11.1%), carbon ink in 192 (7.4%), radar marker in 119 (4.6%), radioactive seed in 18 (0.7%), radiofrequency identification device (RFID) in 12 (0.5%), or other methods in two (0.1%). One TLN was marked in 2,427 patients (93.5%), two TLNs in 138 (5.3%), and ≥3 in 27 patients (1%). Targeted removal of the TLN was planned in 2,100 patients (80.9%; TAD in 2,076 [80.0%] and TLNB in 24 [0.9%]). The TLN was detected and removed by TAD/TLNB in 1,915 patients (91.2%). TLN detection rate was the highest in patients whose TLNs were marked pre-NACT with markers suitable for probe-guided detection (96.6%; radioactive seed: 100%, magnetic seed: 96.9%, radar marker: 96.1%, RFID: 90%), followed by carbon ink (94.9%) and clip (89.6%; $P < .001$).

CONCLUSION This large prospective analysis of patients with initially clinically node-positive BC receiving NACT demonstrates that probe-guided detection markers used to mark metastatic nodes before NACT provide superior detection rates.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Accepted December 4, 2025
Published January 21, 2026

J Clin Oncol 00:1-11

View Online Article

INTRODUCTION

The optimal axillary surgical staging technique in patients with breast cancer (BC) who are initially node-positive and convert to clinically negative node status through neoadjuvant chemotherapy (NACT) has been the subject of debate in the past years.[1-3] In many countries, axillary lymph node dissection (ALND) as the method of choice has been

CONTEXT

Key Objective
How reliable is the detectability of axillary target lymph nodes after neoadjuvant chemotherapy in breast cancer, depending on the type of marker used?

Knowledge Generated
The highest detection rates in the prospective AXSANA study of over 90% were seen for markers suitable for probe-guided detection and carbon suspension. Nodes marked with clips were detectable in <90% of cases after neoadjuvant chemotherapy.

Relevance *(A.M. Thompson)*
Accurate assessment of axillary node involvement after neoadjuvant chemotherapy is key to selecting further treatment and prognostic for outcomes.*

*Relevance section written by *JCO* Consulting Editor Alastair M. Thompson, BSc(Hons), MBChB, MD, FRCSEd, FACS.

replaced by less extensive techniques, such as sentinel lymph node biopsy (SLNB) or a combination of SLNB and removal of a metastatic target lymph node (TLN) marked before NACT, the latter referred to as targeted axillary dissection (TAD).[4-11] When compared with SLNB alone, TAD can reduce the false-negative rate (FNR) from approximately 12%-14% to 2%-9%.[1,10,12-17] However, uncertainty remains regarding the best marking technique employed pre-NACT, and commonly used options range from clips and coils, through carbon ink to probe-guided detection on the basis of different mechanisms such as magnetism, radar reflection, radiofrequency, or radioactivity.[1,12,18-23]

The clinically most relevant aspect in this context is the reliable identification of the marked target node, especially in patients achieving clinical and radiologic response in the axilla, that is, when the lymph node metastasis itself can no longer serve as a visualizable target.[24] Importantly, metallic clips usually require an additional post-NACT preoperative localization procedure, for example, placement of a wire or a localization device, which may result in logistical challenges and discomfort for the patient. Furthermore, the risk of localization failure because of lack of clip visibility on imaging may be as high as 20%.[10,25] By contrast, probe-guided detection markers placed pre-NACT allow the patient to directly proceed to surgery following NACT without further interventions. Similarly, carbon injection into the TLN before NACT does not require a separate localization procedure either and allows visual identification of the marked node. Previously reported detection rates for these techniques are in the range of 90%-98%,[12,14,15] but comparative data regarding TLN detection rates among different methods are not available.

The present analysis aimed at examining the detection rate and the number of removed lymph nodes at TAD/TLNB using different pre-NACT TLN marking techniques in the largest available cohort of patients with BC enrolled in the international prospective AXSANA study.

MATERIALS AND METHODS

The design of the ongoing AXSANA study[26] (NCT04373655) has been described elsewhere.[1,22,27] Briefly, AXSANA is an international, multicenter, prospective cohort study initiated by the European Breast Cancer Research Association of Surgical Trialists (EUBREAST e.V). Patients with initially cN+ BC who receive at least four cycles of NACT are eligible. Minimally invasive biopsy of lymph nodes was mandatory until an amendment on October 10, 2020. Since then, minimally invasive biopsy is optional. In case of a negative or inconclusive minimally invasive biopsy of axillary lymph node(s), patients can be included only if the final classification after imaging-pathology correlation is cN+. Axillary staging is performed according to institutional and national standards and may include ALND, SLNB, TAD, or TLN biopsy (TLNB). Coprimary end points are invasive disease-free survival (iDFS), axillary recurrence rate, health-related quality of life, and arm morbidity. The study is statistically powered to detect differences in iDFS and axillary recurrence rate between different surgical staging techniques. The main goal is to establish noninferiority of less extensive axillary staging (TAD, TLND, and SLNB) versus ALND with regard to iDFS. Enrollment began in June 2020. The trial fulfills high-quality standards, with 100% of the data entries being remotely monitored by experienced breast surgeons. Performance of different marking techniques, MRI artifacts, dislocation and localization failure rates, and lost marker rates are predefined secondary end points of the study. All currently available marking techniques for the TLN are allowed.

The current prospectively planned subgroup analysis includes patients who had TLN marking before NACT (pre-NACT) and who had undergone axillary surgery by January 6, 2025.

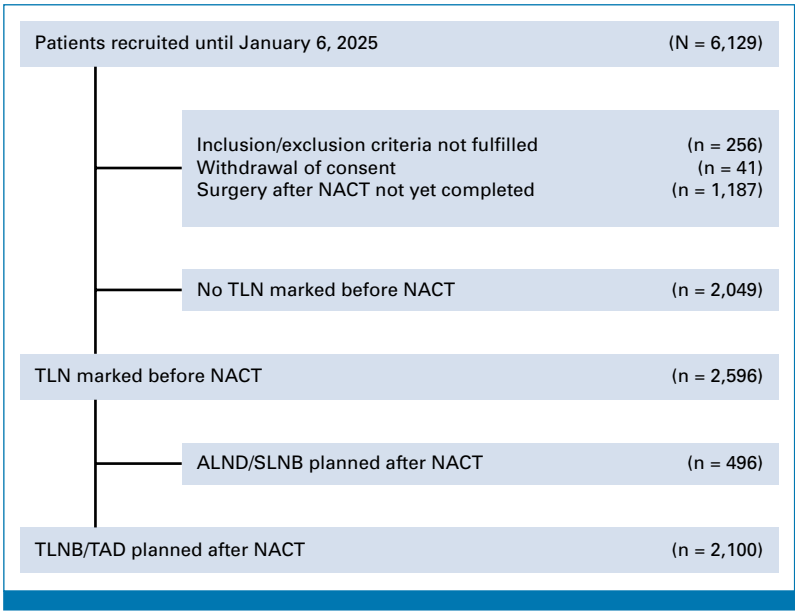

FIG 1. Flowchart of AXSANA study cohort included until January 6, 2025. ALND, axillary lymph node dissection; NACT, neoadjuvant chemotherapy; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection; TLN, target lymph node; TLNB, target lymph node biopsy.

Node status at diagnosis and after NACT was assessed clinically according to institutional standards without study-specific imaging requirements. Pathologic complete response (pCR) was defined as the absence of invasive tumor cells in the breast and axilla. Thus, the presence of isolated tumor cells in lymph nodes (ypN0[i+]) was defined as non-pCR for this analysis.[28] Patients are grouped according to the marker placed pre-NACT into the TLN into one of the following groups: clip, probe-guided, carbon, and combination of marking techniques.

For descriptive analysis, absolute frequencies are reported for categorical variables and means ± standard deviations (SD) or median values (IQR) for continuous variables. Mean values were compared using the Kruskal-Wallis test, and frequencies of categorical variables using the chi-square or Fisher exact test and the Cochrane-Armitage test for ordinal variables. *P* values <.05 were considered statistically significant unless noted otherwise. TLN detection rate was defined as the proportion of patients with successful identification and removal of marked lymph node(s) by TAD/TLNB. Determinants of a nondetection of TLN were evaluated by regressing TLN detection results (successfully identified and removed = no *v* yes) on clinicopathologic parameters among patients with a planned TAD or TLNB. Owing to very few missing data (≤0.6% of patients per variable) complete case analysis was performed as primary analysis. All univariable and multivariable binary logistic regression analyses included 2,022 patients with nonmissing values for all variables. As a sensitivity analysis, we used multiple imputation by chained equations with 50 imputed data sets and 30 iterations. The multivariable analyses included all variables with a least one univariably significant (≤0.10) coefficient. Odds ratios and 95% CI were calculated. Statistical analyses were performed using SPSS version 27 (IBM, Armonk, NY) and R version 4.3.1 (GNU General Public License). The statistical analyses and the presentation of the results were carried out following the recommendations of the STROBE guideline for observational studies.[29]

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University Aachen, Germany (Date: April 28, 2020, Number: EK 013/20).

Consent to Participate

Informed consent was obtained from all individual participants included in this study.

RESULTS

Characterization of the Study Cohort

In total, 6,129 patients from 288 sites in 26 countries were enrolled in the AXSANA study at the time of analysis. Of them, 2,596 had at least one TLN marked before NACT and had completed surgical treatment until January 6, 2025 (Fig 1). The clinicopathologic characteristics of these patients are shown in Table 1. The median number of suspicious lymph nodes before NACT was two and 13.3% of patients had four or more suspicious nodes. A total of 2,484 patients

TABLE 1. Clinicopathologic Characteristics of the Study Cohort With TLN Marking Before NACT

Characteristic	Patients (N = 2,596), No. (%)
Mean age, years (±SD)	51.9 (±11.9)
Mean BMI, kg/m^2 (±SD)	26.4 (±7.8)
Clinical tumor stage at diagnosis, No. (%)	
cT1	659 (25.4)
cT2	1,613 (62.1)
cT3	290 (11.2)
cT4	34 (1.3)
No. of suspicious lymph nodes before NACT, No. (%)	
1-3	2,239 (86.6)
≥4	346 (13.4)
Missing, n = 11	
Histopathologic tumor type, No. (%)	
Ductal	2,387 (92.0)
Lobular	120 (4.6)
Mixed ductal and lobular	24 (0.9)
Other	64 (2.5)
Missing, n = 1	
Histologic grading, No. (%)	
1	54 (2.1)
2	1,103 (42.6)
3	1,425 (55.1)
4	5 (0.2)
Missing, n = 9	
Tumor subtype, No. (%)	
HR+/HER2−	1,174 (45.2)
HR+/HER2+	588 (22.7)
HR−/HER2+	298 (11.5)
HR−/HER2−	536 (20.6)
Tumor multicentricity, No. (%)	
Yes	349 (13.4)
No	2,247 (86.6)
Clinical tumor stage after NACT, No. (%)	
ycT0	1,028 (39.8)
ycT1	1,124 (43.5)
ycT2	376 (14.5)
ycT3	45(1.7)
ycT4	12 (0.5)
Missing, n = 11	
Clinical lymph node stage after NACT, No. (%)	
ycN0	1,895 (73.1)
ycN+	697 (26.9)
Missing, n = 4	
Type of breast surgery, No. (%)	
Breast-conserving surgery	1,755 (67.9)
Mastectomy	828 (32.1)
Missing, n = 13	
Pathologic tumor stage after NACT, No. (%)	
ypT0	1,015 (39.1)
ypTis	146 (5.6)
ypT1	888 (34.2)
ypT2	412 (15.9)
ypT3	123 (4.7)
ypT4	12 (0.5)
Pathologic lymph node status after NACT, No. (%)	
ypN0	1,365 (52.6)
ypN0(i+)	44 (1.7)
ypN1mi	132 (5.1)
ypN1	748 (28.8)
ypN2	252 (9.7)
ypN3	54 (2.0)
ypNX	1 (0.1)
pCR (ypT0/is and ypN0) after NACT, No. (%)	
Yes	992 (38.2)
No	1,604 (61.8)

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; NACT, neoadjuvant chemotherapy; pCR, pathologic complete response; SD, standard deviation; TLN, target lymph node.

(95.7%) underwent a minimally invasive biopsy of one or more nodes (Appendix Table A1, online only). The minimally invasive biopsy was positive in 2,380 (95.8%) patients. In 1,471 patients (59.2%), the cytology/pathology report was available before pre-NACT TLN marking. The median time between node biopsy and marker placement was 8 days (Appendix Table A2).

Marking of Target Lymph Nodes

Pre-NACT TLN marking was performed using a clip in 2,003 patients (77.2%), a magnetic seed in 287 (11.1%), carbon ink in 192 (7.4%), radar marker in 119 (4.6%), radioactive seed in 18 (0.7%), radiofrequency identification device (RFID) in 12 (0.5%), or other methods in two patients (0.1%). More than

TABLE 2. Types of Combined TLN Marking Pre-NACT (n = 36)

Marker Combination	No. (%)
Clip + carbon	17 (47.2)
Clip + magnetic seed	7 (19.4)
Clip + radar marker	3 (8.3)
Clip + radioactive seed	1 (2.8)
Magnetic seed + carbon	7 (19.4)
Clip + carbon + radioactive seed	1 (2.8)
Total	36 (100)

Abbreviations: NACT, neoadjuvant chemotherapy; TLN, target lymph node.

TABLE 3. TLN Detection Rate and Lymph Node Retrieval in Patients Receiving Different Marking Techniques Pre-NACT

Pre-NACT Marking Technique	No. of Patients	TLN Detection Rate, %	No. of Removed Nodes at TAD/TLNB (mean ± SD)	Total No. of Removed Lymph Nodes (mean ± SD)	Total No. of Removed Lymph Nodes in Patients Receiving cALND (n = 795; mean ± SD)
Clip	1,594	89.6	2.95 ± 1.90	7.48 ± 5.96	12.83 ± 5.82
Carbon	118	94.9	2.99 ± 1.73	6.35 ± 4.71	10.68 ± 3.91
Markers suitable for probe-guided detection	355	96.6	2.81 ± 1.73	7.39 ± 6.27	13.79 ± 5.81
Magnetic seed	225	96.9	2.77 ± 1.64	7.33 ± 6.21	13.95 ± 5.91
Radar marker	102	96.1	3.10 ± 2.01	6.71 ± 5.24	12.69 ± 4.48
Radioactive seed	16	100	1.88 ± 0.72	11.50 ± 8.11	17.10 ± 4.01
RFID	10	90	2.40 ± 1.08	10.20 ± 10.76	20.25 ± 11.00
Other	2	100	2.00 ± 0.00	2.00 ± 0.00	NA
Combined	33	93.9	2.76 ± 1.42	7.94 ± 5.21	11.39 ± 4.59
Total	2,100	91.2	2.92 ± 1.86	7.41 ± 5.94	12.85 ± 5.75

Abbreviations: cALND, completion axillary lymph node dissection; NA, not applicable; RFID, radiofrequency identification device; SD standard deviation; TAD, targeted axillary dissection; TLN, target lymph node; TLNB, target lymph node biopsy.

one type of marker was placed in 36 patients (1.4%; Table 2). One TLN was marked in 2,427 patients (93.5%), followed by two TLNs in 138 (5.3%) and ≥3 in 27 patients (1%). The mean number of marked lymph nodes was 1.07 ± 0.30 and differed significantly between the groups receiving the different marking methods ($P < .001$). The mean number of marked TLNs was the highest if carbon ink was used (mean 1.23 ± 0.55), followed by combined marking (1.14 ± 0.35), clip (1.07 ± 0.28), magnetic seed (1.06 ± 0.25), and radar marker (1.03 ± 0.21); no patient received more than one radioactive seed or RFID. Marking was performed under ultrasound guidance in 2,558 procedures (98.5%), while other imaging techniques were used in 33 patients (1.3%; missing in five patients, 0.2%).

Axillary Surgery

Of 2,596 patients, 2,100 (80.9%) patients with TLNs marked pre-NACT were scheduled for TLN removal after NACT: 2,076 (80.0%) for a TAD and 24 (0.9%) for a TLNB. In patients scheduled for a TAD, the SLN was marked with a single tracer in 1,711 patients (82.4%; technetium n = 1,345, SPIO n = 183, dye n = 153, ICG n = 29, other n = 1) and with dual tracers in 347 (16.7%). Different combinations of SLN tracer and TLN markers are presented in Appendix Table A3. At least one SLN was removed in 1,939 of 2,076 patients (93.4%) with planned TAD. A median of two SLNs (IQR, 1-3) was removed as part of the TAD. In 1,332 of 2,076 patients (64.2%), at least one lymph node was both SLN and TLN. In 795 patients with planned TAD/TLNB (37.9%), a completion ALND (cALND) was performed. Among these patients, cALND was conducted during the same surgery in 552 patients (69.4%) and as a secondary procedure in 243 (30.6%). Of 552 patients undergoing cALND during the same surgery, frozen section was performed in 370 patients (67.0%). The median number of removed lymph nodes was 2 (IQR, 2-5) without and 12 (IQR, 9-16) with cALND.

Detection and Removal of Target Lymph Nodes

TLN was detected and removed during TAD/TLNB in 1,915 of 2,100 patients (91.2%). The median number of TLN removed was 1 (IQR, 1-1). In 378 patients (18.0%), more than one TLN was detected histologically. The detection rate differed significantly between the markers used pre-NACT ($P = .004$) and was the highest in case of markers suitable for probe-guided detection (96.6% [radioactive seed: 100%, magnetic seed: 96.9%, radar marker: 96.1%, RFID: 90%, other: 100%]), followed by carbon (94.9%), combined marking (93.9%), and clip (89.6%, Table 3). TLN detection rate in patients whose TLN was marked with a clip pre-NACT was numerically higher at study sites that enrolled >20 patients compared with others (91.2% *v* 88.7%). However, this difference was not statistically significant ($P = .118$).

In patients whose TLNs were marked with a clip pre-NACT, different post-NACT preoperative and/or intraoperative localization techniques were documented (Appendix Table A4). In 61 (3.8%) patients, the planned preoperative localization procedure could not be performed because the clip was not visible. In 88 patients (5.5%), the localization procedure was performed but described as questionable because of low visibility of the clip. Of those 88 patients with performed, but questionable, localization procedure, the TLN was detected and removed at TAD/TLNB in 60 patients, resulting in a TLN detection rate of 68.1%.

TAD/TLNB removed a mean number of 2.9 ± 1.9 lymph nodes, which was not significantly different across different TLN marking cohorts ($P = .219$, Table 3). In 67 of 185 patients (36.2%) with TLN not removed during TAD/TLNB, the marker could not be removed either (clips n = 64, carbon n = 2, radar marker n = 1, magnetic seed/radioactive seed/RFID n = 0).

The logistic regression analysis included 1,853 patients with removed TLN and 169 with nonremoved TLN. Univariable and multivariable analyses showed a significantly lower risk of detection failures for the pre-NACT use of probe-guided detection markers and greater experience of the study sites with the marking technique (≥30 procedures). By contrast, the risk of nondetection was higher in obese patients (BMI ≥ 25 kg/m²) and clinically persistent suspicious nodal status after NACT (ycN+; Table 4). The results were similar when missing data were handled by multiple imputation (not shown).

DISCUSSION

To the best of our knowledge, this is the largest prospective study comparing different techniques for pre-NACT marking metastatic TLNs in patients with BC patients scheduled for neoadjuvant chemotherapy. Following the first publication on selective removal of biopsied and marked nodes in 2010,[30] numerous studies have explored the possibility of safely de-escalating the extent of surgical therapy to the axilla.[1,9,10,12,31] So far, most studies have reported on TLN marking using a metallic clip, and this strategy is most commonly employed worldwide. A major limitation of clip-marking, however, is the necessity for a reliable visualization of the marker on preoperative or intraoperative imaging. Here, the method usually requires a separate imaging-guided localization procedure shortly before surgery, mostly guided by ultrasound or, in case of insufficient visibility, mammography, or computed tomography. Consequently, available data suggest a relatively low detection rate of clip-marked TLNs, ranging from 70% to 90% in large studies.[10,25,32,33]

In line with these results, the prospective AXSANA study shows significant differences in detection rates between different pre-NACT marking techniques. The highest detection rate was observed for markers suitable for probe-guided detection (96.6%), followed by carbon (94.9%) and the lowest in patients whose TLN was marked using a clip (89.6%). Although the number of removed lymph nodes was similar across subgroups, pre-NACT use of probe-guided detection markers increased the probability of a successful TLN removal, without affecting the overall number of removed nodes. Because ALND is performed in case of TAD/TLNB failure in most countries, improved TLN detection rates are likely to result in more patients avoiding ALND and consequently in a reduced risk of arm morbidity. Recently, de Wild et al[33] performed a systematic review of TAD procedure using different pre-NACT and post-NACT marking techniques and reported a high identification rate of the TLN in patients whose TLNs were marked with a clip pre-NACT. However, as Siso and Rubio correctly point out in their editorial,[34] it should be noted that 18 of 41 studies excluded patients from the analysis in whom the TLN could not be located preoperatively on imaging, the range of TLN identification on imaging ranging from 49% to 100%, and that exclusion of patients in whom the TLN was not visualized preoperatively may lead to overestimation of the TLN detection rate. For instance, in the nationwide retrospective registry in Denmark, an ultrasound-guided post-NACT preoperative localization procedure was successful only in 79.4% of patients whose TLN was marked with a clip pre-NACT.[35] In the majority of remaining patients, the reason for not performing a localization procedure was the inability to visualize the clip in the lymph node.

The disadvantages of clip-marking may potentially be overcome with the use of ultrasound-visible clips and standardized intraoperative ultrasound. The ILINA study reported on 235 patients with cytology-proven node-positive BC in whom this technique was used.[36] The detection rate of the clipped node was 96% and thus markedly higher than in other studies.[10,25] In this context, it is worth noting that the ILINA study, conducted by the Spanish study group specialized in intraoperative ultrasound,[36,37] suggests that TLN detection in the case of clip marking may be operator dependent. Indeed, TLN detection rates at study sites that enrolled a higher number of patients in the AXSANA study were descriptively but not significantly higher than at other sites. Nevertheless, low experience of the site with the respective marking method was found to be an independent risk factor for nondetection of TLN.

We previously reported that markers are significantly more often lost if clips compared with other marking techniques are used.[38] In this context, the consequences of remaining markers, beyond the risk of leaving residual metastatic nodes, need to be discussed. In case of a clip, no potential complications are expected to arise from a marker left in situ, and most clips are approved for permanent tissue marking.[25] On the other hand, ensuring marker removal in case of probe-guided detection is strongly recommended and may lead to additional imaging and invasive procedures for the patient. Every effort should be made to localize and excise radioactive seeds because of regulatory restrictions on their use. In case of markers likely to cause large artifacts on MRI, such as magnetic and paramagnetic markers as well as RFIDs, leaving a marker behind can result in decreased accuracy of postoperative imaging surveillance.[21,39] The fact that we did not observe radioactive or magnetic markers that have been left in situ suggests that clinicians are aware of the potential consequences of the lost marker situation and are more likely to accept a clip left in situ, compared with other markers.

The detection rate of carbon-marked TLNs observed in the present analysis is similar to previous studies.[14,15] Although the TLN detection rate was higher if a probe-guided detection marker was used, the perceived difference between these markers and carbon ink (96.6% *v* 94.9%) might be of low clinical relevance. Interestingly, although patients receiving carbon marking pre-NACT were more likely to have a higher number of nodes marked compared with patients undergoing other marking methods, possibly reflecting the cost-effectiveness of this approach, the number of node

TABLE 4. Association Between Clinicopathologic Parameters and Nondetection of TLN

Parameter	Overall[a] (N = 2,022)	TLN Removed (n = 1,853)	TLN Not Removed (n = 169)	Univariable Analysis OR (95% CI)	Multivariable[b] Analysis OR (95% CI)
BMI, No. (%)					
≤24.9 kg/m^2	982 (48.6)	916 (93.3)	66 (6.7)	1.0 (ref)	1.0 (ref)
≥25.0 kg/m^2	1,040 (51.4)	937 (90.1)	103 (9.9)	**1.53 (1.11 to 2.11)**	**1.52 (1.10 to 2.12)**
P				**.01**	**.01**
Clinical tumor stage before NACT, No. (%)					
cT1+cT2	1,807	1,656	151	1.0 (ref)	
cT3+cT4	215	197	18	1.00 (0.58 to 1.63)	
P				.99	
No. of suspicious lymph nodes before NACT, No. (%)					
1-3	1,820 (90.0)	1,671 (91.8)	149 (8.2)	1.0 (ref)	
≥4	202 (10.0)	182 (90.1)	20 (9.9)	1.23 (0.73 to 1.97)	
P				.40	
No. of marked lymph nodes before NACT, No. (%)					
1	1,888 (93.4)	1,728 (91.5)	160 (8.5)	1.0 (ref)	
>1	134 (6.6)	125 (93.3)	9 (6.7)	0.78 (0.36 to 1.48)	
P				.48	
Histopathologic tumor type, No. (%)					
Ductal	1,863 (92.1)	1,705 (91.5)	158 (8.5)	1.0 (ref)	
Other	159 (7.9)	148 (93.1)	11 (6.9)	0.80 (0.40 to 1.45)	
P				.49	
Tumor subtype, No. (%)					
HR+/HER2−	884 (43.7)	808 (92.4)	76 (8.6)	1.0 (ref)	
HR+/HER2+	475 (23.5)	433 (21.2)	42 (8.8)	1.03 (0.69 to 1.52)	
HR−/HER2+	241 (11.9)	220 (91.3)	21 (8.7)	1.01 (0.60 to 1.65)	
HR−/HER2−	422 (20.9)	392 (92.9)	30 (7.1)	0.81 (0.52 to 1.25)	
P				.77	
Histologic grading, No. (%)					
1/2	892 (44.1)	815 (91.4)	77 (8.6)	1.0 (ref)	
3/4	1,130 (55.9)	1,038 (91.9)	92 (8.1)	0.94 (0.68 to 1.29)	
P				.69	
Type of marker, No. (%)					
Clip	1,536 (76.0)	1,383 (90.0)	153 (10.0)	1.0 (ref)	1.0 (ref)
Carbon	112 (5.5)	106 (94.6)	6 (5.4)	0.51 (0.20 to 1.09)	0.64 (0.24 to 1.38)
Probe-guided	346 (17.1)	337 (97.4)	9 (2.6)	**0.24 (0.11 to 0.45)**	**0.22 (0.10 to 0.42)**
Combined	28 (1.4)	27 (96.4)	1 (3.6)	0.33 (0.02 to 1.59)	0.32 (0.02 to 1.56)
P				**<.001**	**<.001**
Tumor multicentricity, No. (%)					
Yes	1,770 (87.5)	1,628 (92.0)	142 (8.0)	1.0 (ref)	
No	252 (12.5)	225 (89.3)	27 (10.7)	1.38 (0.87 to 2.09)	
P				.15	
Clinical tumor stage after NACT, No. (%)					
ycT0	878 (43.4)	816 (92.9)	62 (7.1)	1.0 (ref)	1.0 (ref)
ycT ≠ 0	1,144 (56.6)	1,037 (90.6)	107 (9.4)	1.36 (0.98 to 1.89)	1.21 (0.86 to 1.71)
P				.06	.27
Clinical lymph node stage after NACT, No. (%)					
ycN0	1,628 (80.5)	1,506 (92.5)	122 (7.5)	1.0 (ref)	1.0 (ref)
ycN+	394 (19.5)	347 (88.1)	47 (11.9)	**1.67 (1.16 to 2.37)**	**1.56 (1.07 to 2.26)**
P				**<.01**	**.02**

(continued on following page)

TABLE 4. Association Between Clinicopathologic Parameters and Nondetection of TLN (continued)

Parameter	Overall[a] (N = 2,022)	TLN Removed (n = 1,853)	TLN Not Removed (n = 169)	Univariable Analysis OR (95% CI)	Multivariable[b] Analysis OR (95% CI)
No. of previous procedures performed using specific marking technique at study site, No. (%)					
<30	777 (38.4)	696 (89.6)	81 (10.4)	1.0 (ref)	1.0 (ref)
≥30	1,245 (61.6)	1,157 (92.9)	88 (7.1)	**0.65 (0.48 to 0.90)**	**0.62 (0.45 to 0.85)**
P				**.01**	**<.01**
Planned breast surgery, No. (%)					
Breast-conservation	1,454 (71.9)	1,337 (92.0)	117 (8.0)	1.0 (ref)	
Mastectomy	568 (28.1)	516 (90.8)	52 (9.2)	1.15 (0.81 to 1.61)	
P				.42	

NOTE. *P* < .05 are shown in bold.
Abbreviations: HR hormone receptor; HER2 human epidermal growth factor receptor 2; NACT, neoadjuvant chemotherapy; OR, odds ratio; ref, reference; TLN, target lymph node.
[a]All analyses based on 2,022 patients with nonmissing values for all variables in table.
[b]Adjusted for all variables in table.

removed was similar in all cohorts. As carbon ink is more cost effective than other markers and the introduction of the technique does not require any additional technology,[40] it remains a valid alternative, especially for countries with limited financial healthcare resources. A potential advantage of probe-guided detection markers is the transcutaneous signal detection that allows the surgeon to position the skin incision precisely where the TLN is expected to be localized and minimize the dissection effort. In case of carbon ink, the marker is detected visually, and unless a small skin tattoo has been placed above the TLN, the surgeon needs to explore the axilla to find the target.[14,15] Whether this difference affects arm morbidity remains to be clarified as one of the primary end points of the AXSANA study.[1]

The major strengths of this analysis include the fact that results from the largest prospective, multicenter patient cohort available to date are presented. In addition, all data entries in the AXSANA study were continuously monitored by experienced breast surgeons. Nonetheless, our study has several limitations. Marking techniques were not randomized so that confounding is possible. However, multivariable analyses of detection failure including a large number of patient-specific and diagnostic factors demonstrate minimal confounding bias. Despite the large sample size, numbers were sometimes small for specific procedures. Because of the real-world nature of our data, however, such procedures appear to be of relatively low relevance.

Although this analysis focused on a comparison of pre-NACT marking techniques, the AXSANA study is powered to detect differences in survival and quality of life between surgical techniques such as ALND, TAD, SLNB, and TLNB. Indeed, whether marking metastatic nodes before NACT leads to improved clinical outcomes, remains yet to be clarified. So far, the available data showed reduced false-negative rates in patients receiving a TAD or TLNB, compared with SLNB only.[9,10,12,41] On the other hand, increased FNR does not necessarily lead to higher recurrence rates and the evidence on the oncological safety of SLNB only after neoadjuvant therapy has increased in the last years with several studies showing low recurrence rates.[8,11] In particular, the retrospective Omission of Axillary Dissection study showed comparable 3-year cumulative incidence of axillary recurrence between TAD and SLNB (0.5% *v* 0.8%, respectively).[11] In this context, the recent analysis of the B-51 study showed no benefit of regional nodal irradiation (RNI) in patients converting from cN+ to ypN0 status through NACT and favorable outcomes in patients who received SLNB only.[42] In this subgroup, the 5-year invasive cancer recurrence-free interval was 93.5% in patients undergoing RNI and 91.5% in those without RNI.

Further analyses of AXSANA and ongoing trials such as ALLIANCE (ClinicalTrials.gov identifier: NCT01901094), TAXIS,[43,44] ATNEC (ClinicalTrials.gov identifier: NCT04109079), MINIMAX[45] will clarify which staging procedure should be recommended to patients converting from cN+ to ycN0 status, taking into account both the oncologic safety and quality of life.

In conclusion, the use of markers suitable for probe-guided detection for pre-NACT TLN marking results in significantly higher detection rates compared with using clips in patients scheduled to receive a TAD/TLNB after neoadjuvant therapy. Because successful surgical de-escalation in initially node-positive patients depends on a reliable localization and removal of target nodes, we conclude that probe-detectable markers should be used to mark metastatic nodes in patients eligible for a targeted procedure, if available. However, because carbon also showed a high detection rate, this might be a reliable alternative when probe-guided markers are not available.

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PRIOR PRESENTATION

Presented in part at the ASCO Annual Meeting, Chicago, IL, May 30-June 1, 2025.

SUPPORT

Supported by grants from the AGO Breast Study Group (AGO-B-053), the Claudia von Schilling Foundation for Breast Cancer Research, the Ehmann Foundation Savognin, Eugen and Irmgard Hahn Stiftung, Arbeitsgemeinschaft für ästhetische, plastische und wiederherstellende Operationsverfahren in der Gynäkologie e.V. (AWOgyn), EndoMag, Merit Medical, Mammotome, and Sirius Medical.

CLINICAL TRIAL INFORMATION

NCT04373655 (date of registration May 4, 2020)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-01921.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-25-01921.

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ACKNOWLEDGMENT

The authors wish to thank Jessica Wagner, Jana Shabbir, Markus Höing, and Marina Mangold for the coordination of the AXSANA study and all participating study sites for their valuable contribution to this trial. We would also like to thank Dr Sven Thomas-Grasshoff for his contribution to this work and for enrolling patients in the study. For a full list of named collaborators, see the Appendix.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Marking Techniques for Target Lymph Nodes in Node-Positive Breast Cancer Treated With Neoadjuvant Therapy in the AXSANA/EUBREAST-03/AGO-B-053 Study

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Research Funding: Exact Sciences (Inst), Endomag (Inst), CairnSurgical (Inst)
Expert Testimony: PFM Medical
Travel, Accommodations, Expenses: ClearCut Medical, Roche, PFM Medical, Pfizer, Lilly, Daiichi Sankyo Europe GmbH, Gilead Sciences, Jörg Eickeler, AstraZeneca, Exact Sciences, Hexal, Menarini Group, Novartis, MSD Oncology, Zuellig Pharma

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No other potential conflicts of interest were reported.

APPENDIX

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TABLE A1. Minimally Invasive Biopsy of Suspicious Lymph Node(s) in Patients Receiving TLN Marking Pre-NACT

Characteristic	No. (%)
Total	2,596 (100)
Minimally invasive biopsy performed	
Yes	2,484 (95.7)
No[a]	112 (4.3)
Technique of minimally invasive biopsy	
Core biopsy	1,924 (77.5)
Fine-needle aspiration	560 (22.5)
No. of nodes biopsied	
1	2,346 (94.4)
2	98 (3.9)
≥3	27 (1.1)
Unknown	13 (0.5)
Minimally invasive biopsy results	
Positive	2,380 (95.8)
Inconclusive	28 (1.1)
Negative	74 (3.0)
Missing	2 (0.1)
Lymph node metastasis confirmed by minimally invasive biopsy before TLN marking[b]	
Yes	1,471 (59.2)
No	1,003 (40.4)
Missing	10 (0.4)

Abbreviations: NACT, neoadjuvant chemotherapy; TLN, target lymph node.
[a]All patients received marking of at least one TLN, irrespective of whether a minimally invasive biopsy was performed or not.
[b]That is cytology/pathology report available *before* inserting the marker.

TABLE A2. Time Interval Between Node Biopsy, Pre-NACT Marking of the TLN, and Surgery

Measure	Time Between Minimally Invasive Biopsy and TLN Marking, days	Time Between TLN Marking and Surgery, days
Mean	15.3	177.7
Median	8	181
Percentiles		
25th	0	159
75th	23	204

Abbreviations: NACT, neoadjuvant chemotherapy; TLN, target lymph node.

TABLE A3. Combination of Pre-NACT TLN Marking and SLN Marking in Case of a Planned TAD (n = 2,076)

	SLN Tracer[b], No. (%)							
TLN Marker[a]	Dye	Tch	ICG	SPIO	Dual	Other	Missing	Total, No. (%)
Clip	131 (8.3)	1,056 (66.9)	26 (1.6)	87 (5.5)	261 (16.6)	1 (0.1)	16 (1.0)	1,578 (100)
Carbon	7 (6.1)	90 (78.2)	0 (0.0)	0 (0.0)	17 (14.8)	0 (0.0)	1 (0.9)	115 (100)
Magnetic seed	7 (3.1)	85 (37.9)	2 (0.9)	88 (39.3)	41 (18.3)	0 (0.0)	1 (0.5)	224 (100)
Radar marker	1 (1.0)	80 (79.2)	1 (1.0)	0 (0.0)	19 (18.8)	0 (0.0)	0 (0.0)	101 (100)
Radioactive seed	1 (6.3)	14 (87.6)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	16 (100)
RFID	4 (40.0)	0 (0.0)	0 (0.0)	6 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (100)
Other	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)
Combined	2 (6.7)	18 (60.0)	0 (0.0)	2 (6.7)	8 (26.7)	0 (0.0)	0 (0.0)	30 (100)
Total	153 (7.4)	1,345 (64.8)	29 (1.4)	183 (8.8)	347 (16.7)	1 (0.1)	18 (0.8)	2,076 (100)

Abbreviations: ICG, indocyanine green; NACT, neoadjuvant chemotherapy; RFID, radiofrequency identification device; SLN, sentinel lymph node; SPIO, superparamagnetic iron oxide; TAD, targeted axillary dissection; Tch, Technetium; TLN, target lymph node.
[a]Placed before NACT.
[b]All patients were treated according to the institutional and national standard. Therefore, the use of one versus more tracers for SLNB reflects the heterogeneity of recommendations in different countries.

TABLE A4. Post-NACT Pre- and Intraoperative Localization of Clip-Marked Target Lymph Nodes

Localization Method	No. (%)
Total	1,594 (100)
Wire[a]	823 (51.6)
Wire + IOUS[a]	164 (10.3)
IOUS[a]	255 (16)
Radioactive seed	20 (1.3)
Magnetic seed[a]	34 (2.1)
Magnetic seed + IOUS	2 (0.1)
Radar marker	5 (0.3)
Radar marker + IOUS	1 (0.1)
Skin marking only	63 (4.0)
Ink	59 (3.7)
Other	34 (2.1)
Radar marker + wire	1 (0.1)
None	133 (8.3)

Abbreviations: IOUS, intraoperative ultrasound; NACT, neoadjuvant chemotherapy.
[a]In some patients, skin marking was used in addition (wire: 5, wire + IOUS: 2, magnetic seed: 1, intraoperative ultrasound: 30).