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Lost axillary markers after neoadjuvant chemotherapy in breast cancer patients - data from the prospective international AXSANA (EUBREAST 3) cohort study (NCT04373655)

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ABSTRACT

Introduction: Marking metastatic lymph nodes before neoadjuvant chemotherapy (NACT) has become increasingly popular in the surgical treatment of breast cancer. A variety of devices are currently in use. However, the significance of lost markers is poorly understood, and their impact on clinical decisions is unclear.
Materials and methods: Among participants enrolled in the prospective AXSANA cohort study, those planned for target lymph node biopsy (TLNB) or targeted axillary dissection (TAD) with completed post-NACT locoregional therapy (surgery and radiotherapy) by January 21, 2025, were included.
Results: In 88 of 1528 patients (5.8 %), axillary markers could not successfully be removed during surgery after NACT. The lost marker rate differed depending on the marker type (metallic clip/coil 7.0 %, carbon 3.1 %, radar reflector 1.4 %, magnetic seed 0.6 %, radioactive seed 0.0 %, $p < 0.001$). Additional postoperative imaging was performed in 25 (28.4 %) and further surgery to remove axillary markers was performed in 6 (6.8 %) patients with lost markers. The proportion of patients undergoing axillary lymph node dissection (46.6 % versus 36.5 %, p 0.069) and axillary radiotherapy (51.1 % versus 50.2 %, p 0.748) did not differ between patients with and without lost markers. After an average follow-up of 21.8 months, axillary recurrences occurred in 3 patients (3.3 %) with and 16 patients (1.0 %) without lost markers (rate ratio 2.89, p 0.088).
Conclusion: The loss of markers in TLNB/TAD is uncommon and significantly depends on the marking technique. Lost markers may lead to diagnostic uncertainties and additional imaging or surgical procedures.

Abbreviations

SLNB	Sentinel lymph node biopsy
ALND	Axillary lymph node dissection
NACT	Neoadjuvant chemotherapy
FNR	False negative rate
SLN	Sentinel lymph node
TLN	Target lymph node
TLNB	Target lymph node biopsy
TAD	Targeted axillary dissection
MRI	Magnetic resonance imaging
IQR	Interquartile range
SD	Standard deviation
OR	Odds ratio
CI	Confidence interval
BMI	Body mass index
CT	Computed tomography

1. Introduction

Axillary surgery for breast cancer has continuously been de-escalated over the past decades without jeopardizing oncological safety [1]. At the beginning of the 21st century, axillary sentinel lymph node biopsy (SLNB) replaced complete axillary lymph node dissection (ALND) in patients with clinically unsuspicious lymph nodes (cN0) [2]. Arm morbidity is significantly lower after SLNB compared to ALND [3]. Whether such de-escalation of axillary surgery is also safe in patients with initially suspicious, biopsy-proven axillary lymph nodes (cN+), who convert to a clinically node-negative status (ycN0) after neoadjuvant chemotherapy (NACT), is currently under investigation [4]. SLNB in this setting has been associated with a false-negative rate (FNR) exceeding the accepted threshold of 10 %, as demonstrated in several prospective multicenter studies [5–7]. If the most suspicious axillary lymph node, the target lymph node (TLN), is marked before and removed after NACT (target lymph node biopsy, TLNB), the FNR decreases below 10 % [8,9]. A further reduction in the FNR can be achieved by the combined removal of sentinel and target lymph nodes (targeted axillary dissection, TAD) [9–11]. However, in some cases, the TLN and/or axillary marker can not be successfully removed during surgery [12]. Leaving behind an involved TLN could lead to a false-negative result with potential post-neoadjuvant undertreatment and an increased regional recurrence risk. In addition, iodine seeds left in situ are problematic because of radiation exposure [4,8]. Paramagnetic seeds and radar reflectors can impair the assessment of magnetic resonance imaging (MRI) of the breast due to artifacts [13,14]. Residual carbon particles can cause foreign body granulomas [15]. So far, there is no data from prospective studies on risk factors for marker loss and the clinical effects on patients with undetected markers during TLNB/TAD. Consequently, no recommendations are available on how to proceed in patients with lost axillary markers after NACT.

In the international, non-interventional, prospective AXSANA (EUBREAST 03) study, various surgical axillary staging procedures are being compared in initially cN + patients converting to ycN0 after NACT. One of the secondary study objectives is to compare the clinical performance of different marking techniques for the TLN. In addition,

the rate of lost axillary markers and the clinical management of these patients are prospectively recorded [4]. The current report aimed to determine risk factors for lost markers during TAD/TLNB and to assess the clinical and oncological impact of lost axillary markers based on data from the large AXSANA patient cohort.

2. Materials and methods

2.1. AXSANA study

AXSANA (AXillary Surgery After NeoAdjuvant)/EUBREAST 03 (R) (NCT 04373655) is an ongoing prospective international multicentric cohort study, initiated and conducted by the European Breast Cancer Research Association of Surgical Trialists (EUBREAST e.V.) and supported by EUBREAST ETS and the AGO-B study group (AGO-B-053). Since June 2020, patients have been recruited after written consent in 26 countries at 288 study sites. Inclusion criteria are histologically confirmed invasive unilateral breast cancer, age ≥18 years, clinically and/or histologically proven ipsilateral axillary lymph node metastases (minimally invasive lymph node biopsy is recommended but not mandatory for highly suspicious lymph nodes), and completion of at least four cycles of NACT. Exclusion criteria are distant metastases, inflammatory, extramammary, or recurrent breast cancer, supraclavicular lymph node metastases, and pregnancy/breastfeeding. Primary study objectives are a comparison of different surgical staging procedures in the axilla after NACT (TLNB, SLNB, TAD, ALND) with regards to invasive disease-free survival, axillary recurrence rate, health-related quality of life, and arm morbidity for patients who achieve conversion to ycN0 after NACT [16]. Documentation by the study sites is performed in the eCRF documentation system of the AXSANA study using REDCap® software (Department of Biomedical Informatics, Vanderbilt University, Nashville, TN, USA). All data sets are checked for completeness and plausibility as part of remote monitoring.

2.2. Study cohort

This analysis includes all patients enrolled in the AXSANA study until January 21, 2025, in whom a TLN was marked before NACT, a TLNB or TAD was planned for axillary staging, and whose locoregional therapy (surgery ± radiotherapy) was completed (Fig. 1). The aim was to determine the frequency of axillary marker loss (i.e. the axillary marker cannot be reliably removed during axillary surgery and is either still in the patient or its location is unclear), to assess clinicopathological factors associated with an increased risk of lost markers, and to analyze the individual management by the study sites in case of a lost marker. Finally, we compared the axillary recurrence rates for patients with and without lost markers.

2.3. Statistical analysis

For the descriptive analysis to characterize the study population, absolute and relative frequencies were reported for categorical parameters, and mean values ± standard deviations (SD) or median values (interquartile range, IQR) for continuous parameters. The cohorts with and without lost markers were tested for significant differences in the clinicopathological parameters using the Mann-Whitney *U* test (continuous) or chi-square test (categorical). The axillary recurrence rate between the groups with and without lost markers was compared using a log-rank test. Clinicopathologic variables available before surgery with potential impact on the detectability of the axillary marker during surgery were included in the univariable and multivariable binary logistic regression to examine their potential impact on the risk of a lost axillary marker (only patients with non-missing values for all variables were included). Odds ratios (OR) and corresponding 95 % confidence intervals (CIs) were calculated for each variable. All variables with a p-value <0.05 were considered statistically significant. Statistical analysis was performed using SPSS® version 27 (IBM, Armonk, New York, USA) and R version 4.3.1 (GNU General Public Licenses).

3. Results

3.1. Study cohort

Between June 1, 2020, and January 21, 2025, 6200 patients were recruited into the AXSANA study. The present analysis included 1528 study participants in whom removal of the TLN was planned as part of a TLNB (n = 23, 1.5 %) or TAD (n = 1,505, 98.5 %) after completion of NACT and whose locoregional therapy (surgery ± radiotherapy) had been completed. In 88 patients (5.8 %), axillary markers could not successfully be removed during surgery (Fig. 1). In 20 of these patients

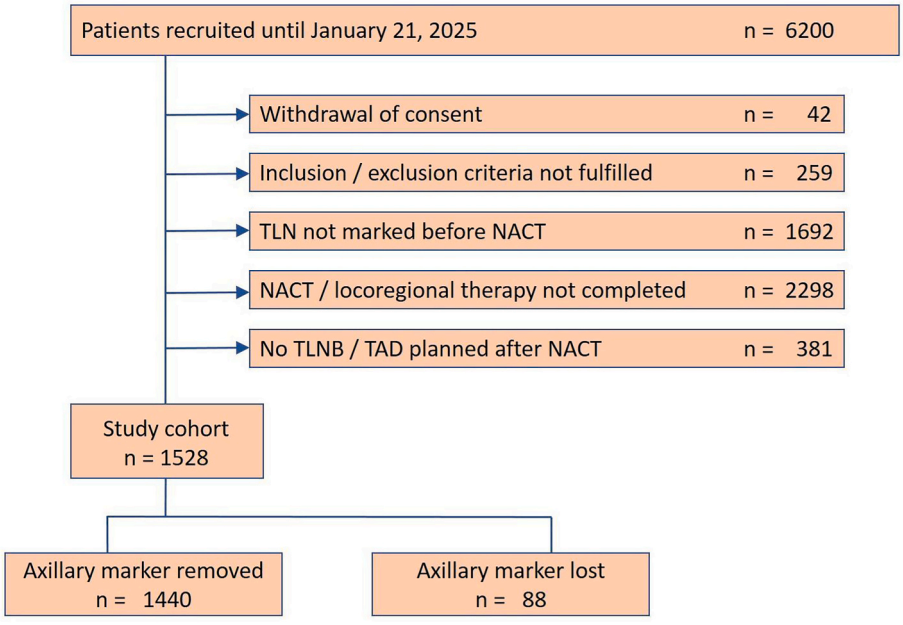

Fig. 1. Study flowchart.

(22.7 %) the lost marker was left in the patient, in 59 (67.0 %) the location of the undetected marker was unclear, and in 8 (9.9 %), the marker was reported to be outside of the patient's body (information on the fate of the marker was missing for one patient, 1.1 %).

The mean age in the cohort was 51.3 years (±11.6), and the mean body mass index (BMI) was 26.3 kg/m^2 (±9.1). Metal clips were the most frequently used marker type (n = 1,173, 76.8 %) (Table 1).

At least one TLN was removed in 1455 of the 1528 patients (95.2 %). In 40 out of 88 patients with a lost marker (45.5 %), an assumed TLN was removed, but the applied marker was not identified (clip n = 37, carbon n = 1, magnetic seed = 1, combined clip and carbon n = 1). Among 1505 study participants with planned TAD, at least one SLN was detected in 1407 cases (93.5 %). The median number of removed lymph nodes (TLN/SLN ± ALND) was 6 (IQR, 3–10) and did not differ between patients with successfully removed (median 5, IQR 3–10) and those with lost markers (median 7, IQR 3–11) (p 0.354). In the overall cohort, the median number of removed SLN/TLN was 2 (IQR, 2–4). However, the number of removed TLN/SLN was significantly higher in patients with successful marker removal compared to patients with lost markers (median 3 (IQR, 2–4) versus 2 (IQR, 1–3) (p 0.003).

3.2. Risk factors for lost markers

The lost marker rate for metal clips was 7.0 % (n = 82/1173), for carbon 3.1 % (n = 3/97), radar reflectors 1.4 % (n = 1/69), paramagnetic seeds 0.6 % (n = 1/159), radioactive iodine seeds 0.0 % (n = 0/2), and others 0.0 % (n = 0/5). Other markers included magnetic seeds in 2 and radiofrequency identification tags (RFID) in 3 cases. In 23 patients, multiple markers were applied (clip + carbon n = 10, clip + paramagnetic seed n = 5, carbon + paramagnetic seed n = 5, clip + radar reflector n = 2, clip + carbon + radioactive iodine seed n = 1). The clip could not be removed in one patient (4.3 %) in whom the clip and carbon were combined. Of 1528 patients, 56 (3.6 %) were excluded from the regression analysis because they had a missing value for at least one of the variables. Table 2 shows the results of the univariable and multivariable analyses of the 1472 complete cases. The multivariable analysis showed a significantly lower risk of marker loss when markers other than clips were used (OR 0.24, 95 % CI 0.09–0.51, p < 0.001), if a mastectomy was planned instead of breast-conserving surgery (OR 0.52, 95 % CI 0.27–0.94, p 0.03), and if the study site had previously performed at least 30 TAD/TLNB procedures with the relevant marking procedure (OR 0.59, 95 % CI 0.38–0.93, p 0.02). On the contrary, the risk of lost markers was increased if no complete clinical remission was achieved in the breast (OR 2.02, 95 % CI 1.23–3.40, p 0.006).

3.3. Clinical management of lost markers

In 25 of the 88 patients (28.4 %) with a lost marker, additional imaging was performed to detect the marker. In 23 patients, one additional procedure was performed: ultrasound (n = 3), computed tomography (CT) (n = 11), X-ray (n = 7), or mammography (n = 2). Two patients underwent two additional examinations each (ultrasound and mammography n = 1, chest X-ray and CT n = 1). Additional imaging identified the marker in 16 out of 25 patients (64.0 %). In 3 patients with a lost clip and one patient with a lost radar reflector, the marker was not detected by imaging, and it was concluded that it was no longer in the patient (Table 3). In 6 patients (6.8 %), further surgery was performed to remove the lost marker.

The proportion of patients undergoing axillary lymph node dissection (46.6 % versus 36.5 %, p 0.069) and axillary radiotherapy (51.1 % versus 50.2 %, p 0.748) did not differ between patients with and without lost markers.

3.4. Oncological outcomes

The mean follow-up time was 21.8 (±9.8) months. Axillary

Table 1
Clinicopathological characteristics of the study cohort.

Parameter	Overall (n = 1528)	Marker removed (n = 1440)	Marker lost (n = 88)
Mean age, years (±SD)	51.3(±11.6)	51.3(±11.7)	51.4(±10.6)
Mean body mass index, kg/m^2(±SD)	26.3(±9.1)	26.3(±9.4)	25.5(±4.2)
Clinical tumor stage before NACT, n(%)			
cT1	411(26.9)	382(26.5)	29(33.0)
cT2	967(63.3)	920(63.9)	47(53.4)
cT3	137(8.9)	126(8.8)	11(12.5)
cT4	13(0.9)	12(0.8)	1(1.1)
Number of suspicious lymph nodes before NACT, n(%)			
1–3	1365(89.3)	1284(89.2)	81(92.0)
≥4	163(10.7)	156(10.2)	7(8.0)
Number of marked lymph nodes before NACT, n(%)			
1	1424(93.2)	1342(93.2)	82(93.2)
2	86(5.6)	80(5.6)	6(6.8)
3	15(1.0)	15(1.0)	0(0.0)
Missing	3(0.2)	3(0.2)	0(0.0)
Histopathological tumor type, n(%)			
Ductal	1411(92.3)	1328(92.2)	83(94.3)
Lobular	68(4.5)	64(4.4)	4(4.5)
Mixed ductal and lobular	11(0.7)	11(0.8)	0(0.0)
Other	37(2.4)	36(2.5)	1(1.1)
Missing	1(0.1)	1(0.1)	0(0.0)
Tumor subtype, n (%)			
HR+/HER2-	666(43.6)	630(43.8)	36(40.9)
HR+/HER2+	360(23.5)	334(23.2)	26(29.5)
HR-/HER2+	195(12.8)	187(13.0)	8(9.1)
HR-/HER2-	307(20.1)	289(20.0)	18(20.5)
Histological grading, n(%)			
1	40(2.6)	39(2.7)	1(1.1)
2	646(42.3)	605(42.0)	41(46.6)
3	835(54.7)	789(54.8)	46(52.3)
4	2(0.1)	2(0.1)	0(0.0)
Missing	5(0.3)	5(0.4)	0(0.0)
Type of marker, n(%)			
Carbon	97(6.4)	94(6.5)	3(3.5)
Radioactive seed	2(0.1)	2(0.1)	0(0.0)
Paramagnetic seed	159(10.4)	158(11.0)	1(1.1)
Radarmarker	69(4.5)	68(4.7)	1(1.1)
Clip	1173(76.8)	1091(75.8)	82(93.2)
Other	5(0.3)	5(0.4)	0(0.0)
Combined	23(1.5)	22(1.5)	1(1.1)
Tumor multicentricity, n(%)			
Yes	193(12.6)	183(12.7)	10(11.4)
No	1335(87.4)	1257(87.3)	78(88.6)
Clinical tumor stage after NACT, n(%)			
ycT0	660(43.2)	632(43.9)	28(31.8)
ycT1	656(42.9)	609(42.3)	47(53.4)
ycT2	188(12.3)	177(12.3)	12(13.6)
ycT3	17(1.1)	16(1.1)	1(1.2)
ycT4	2(0.1)	2(0.1)	0(0.0)
Missing	5(0.3)	5(0.3)	0(0.0)
Clinical lymph node stage after NACT, n(%)			
ycN0	1246(81.6)	1176(81.7)	70(79.5)
ycN+	280(18.3)	262(18.2)	18(20.5)
Missing	2(0.1)	2(0.1)	0(0.0)
Planned axillary surgery, n(%)			
TLNB	23(1.5)	22(1.5)	1(1.1)
TAD	1505(98.5)	1418(98.5)	87(98.9)
cALND performed			
yes	567(37.1)	526(36.5)	41(46.7)
no	961(62.9)	914(63.5)	47(53.4)
Experience in conducting TAD, n(%)			
≥30	886 (58.0)	844 (58.6)	42 (47.7)
<30	606 (39.7)	563 (39.1)	43 (48.9)
Missing	35 (2.3)	33 (2.3)	3 (3.4)
Planned breast surgery, n(%)			
Breast-conserving surgery	1112 (72.8)	1041 (72.3)	71 (80.7)
Mastectomy	416 (27.2)	399 (27.7)	17 (19.3)
Final result of breast surgery, n(%)			

(continued on next page)

Table 1 (*continued*)

Parameter	Overall (n = 1528)	Marker removed (n = 1440)	Marker lost (n = 88)
Breast-conserving surgery	1089(71.3)	1022(71.0)	67(76.1)
Mastectomy	430(28.1)	410(28.5)	20(22.7)
Missing	9(0.6)	8(0.5)	1(1.1)
Pathological lymph node status after NACT, n(%)			
ypN0	865(56.6)	810(56.3)	55(62.5)
ypN0i+	32(2.1)	32(2.2)	0(0.0)
ypN1mi	74(4.8)	71(4.9)	3(3.4)
ypN1	423(27.7)	399(27.7)	24(27.3)
ypN2	115(7.5)	111(7.7)	4(4.5)
ypN3	18(1.2)	16(1.1)	2(2.3)
ypNX	1(0.1)	1(0.1)	0(0.0)
pCR (ypT0/is +ypN0) after NACT, n(%)			
Yes	629(41.2)	591(41.0)	38(43.2)
No	899(58.8)	849(59.0)	50(56.8)

SD standard deviation; NACT neoadjuvant chemotherapy; HR hormone receptor; HER2 human epidermal growth factor receptor 2; TLNB target lymph node biopsy; TAD targeted axillary dissection; cALND completion axillary lymph node dissection; pCR pathologic complete response.

recurrences occurred in 3 patients (3.3 %) with and 16 patients (1.0 %) without lost markers (rate ratio 2.89, p 0.088).

Of the 48 patients in whom neither marker nor TLN could be removed, at least one SLN was detected in 41 (85.4 %). The remaining 7 patients had no lymph node metastases in the ALND (ypN0).

Of the 41 patients with marker loss who underwent ALND, 21 (47.7 %) were finally ypN+. In 6 of them, a TLN had been removed despite a lost marker, and in all of these cases, the TLN was found to be metastatic.

4. Discussion

To the best of our knowledge, this is the first prospective study that assesses the frequency and clinical/oncological impact of lost axillary markers in initially node-positive breast cancer patients undergoing TLNB or TAD for axillary staging after NACT. Overall, the loss of axillary markers is a rare event. However, if metal clips are used to mark the TLN, the risk of marker loss is higher compared to other techniques. To date, there has only been one retrospective single-center study in which the problem of lost markers in association with TLNB/TAD was addressed. In this study, a clip could not be removed during surgery in 10 of 30 (33 %) patients [17]. Sonographic evaluations during NACT show that the metal clip dislocates from shrinking lymph nodes into the perinodal tissue in up to 30 % of cases [18]. Marker dislocation into the tissue surrounding the lymph node has been rarely described with probe-based detectable markers, which could explain their low risk of loss [14,19]. Dislocation of carbon suspension into the perinodal tissue is excluded due to the application technique [20,21]. Therefore, non-detection of the carbon always means non-detection of the TLN.

From an oncological perspective, the surgeon's statement (documented in the case report form) that the TLN was removed despite marker loss should be interpreted with caution. Finally, only the marker detection within a removed lymph node or the histological detection of a marker bed in the lymph node confirms the removal of the initially marked, metastatically affected TLN. However, in the current analysis, we did not observe an increased axillary recurrence risk in patients with lost markers. In patients with an undetected TLN, at least one SLN was identified in the majority of patients with planned TAD. Secondary ALND performed for uncertainties, if the TLN was resected, did not identify any missed axillary metastasis in our series. Therefore, a lost marker should not automatically be a reason to perform an ALND if at least one TLN or one SLN could be removed.

Nevertheless, marker loss may cause anxiety and have further adverse implications for patients. Due to diagnostic uncertainties, some patients (a quarter of those affected in the AXSANA study) undergo additional imaging procedures. These are not only harmful for the patients due to radiation exposure, but may also lead to further invasive procedures to identify and remove the marker. In addition, it is not certain whether all markers can be detected using imaging procedures. Depending on the slice thickness of the CT scans, small clips may be missed on imaging, the axilla may not be completely captured on mammography [17], or it may no longer be possible to visualize axillary clips sonographically after NACT [18].

However, potential long-term marker-specific complications associated with their retention in situ must also be considered, mainly with probe-based marking systems. In many countries, the use of radioactive iodine seeds for diagnostic purposes is not permitted at all or only for a limited period [4]. In the case of a lost radioactive seed, both an unclear fate and remaining in situ with a long half-life of 59.6 days [8] would be problematic in terms of radiation protection regulations. In our analysis, not a single patient with iodine seed was affected by a lost marker situation, but this type of TLN labeling was only used in 2 patients. In the largest study on TLN marking with radioactive iodine seeds published to date, the prospective RISAS study, successful TAD was reported in 223 of 227 patients (98.2 %), but no statement was made about the fate of the iodine seed in the event of unsuccessful TAD [11]. Paramagnetic markers can complicate the assessment of magnetic resonance imaging (MRI) by causing 4-6 cm-sized artifacts [22]. Even when these markers are placed in the axilla and not in the breast, this causes limitations in the assessability of a breast MRI in 48 % of patients [13]. Therefore, if a breast MRI is necessary in follow-up, a lost axillary paramagnetic seed may be disadvantageous. Radar reflectors also cause artifacts in breast MRI when inserted in the axilla [14]. However, these artifacts are significantly smaller (<5 mm) [23] and therefore affect the MRI evaluation less frequently, namely in only 3.7 % [14]. Although the current study shows only a very low risk of lost markers when using paramagnetic seeds and radar reflectors (0.6 and 1.4 %, respectively), this risk should be addressed with the patient if breast MRI is planned during follow-up. Carbon can cause foreign body granulomas if it remains in the body for a long time [15,24]. Therefore, a complete removal of the carbon-marked tissue is recommended [21]. In the breast, these granulomas can simulate a malignancy on imaging and lead to further clarifying measures [24–26]. Whether this also applies to the long-term retention of carbon particles in the axilla is still unclear.

The advantage of the present study is the prospective, multicenter study design, in which the use of all markers available for TLN labeling is permitted. Therefore, for the first time, it was not only possible to evaluate the clinical procedure for lost markers in a real-world setting, but also to identify risk factors for lost axillary markers. Limitations arise for the evaluation of the axillary recurrence rate due to the comparatively short mean follow-up of 21.8 months. Since the majority of axillary recurrences occur within 36 months after surgery (depending on subtype) [27], a re-evaluation should be performed after this period. Since only patients with planned TAD/TLNB were included in the current analysis, patients who underwent ALND due to a clip that could not be visualized on imaging after NACT were excluded. This selection is because the removal of the TLN/marker is not routinely investigated during ALND.

5. Conclusion

Marker loss following TLNB/TAD is uncommon and significantly influenced by the marking technique used. While it appears to have little impact on the oncologic outcome, such adverse events can cause clinical uncertainties, marker type-specific long-term disadvantages, and additive diagnostic and invasive procedures. Additional surgeries for marker removal should not be routinely performed. Instead, a thorough interdisciplinary discussion seems necessary to assess the reliability of axillary staging. The detection and removal rate is a key endpoint for comparing different markers for TLNB/TAD.

Table 2
Association between clinicopathological parameters and risk for lost axillary marker.

Parameter	Overall (n = 1472)	Marker removed (n = 1387)	Marker lost (n = 85)	Univariable analysis OR (95 % CI)	Multivariable analysis OR (95 % CI)
Body mass index, n(%)					
<25.0 kg/m^2	721(49.0)	674(93.5)	47(6.5)	1.0(ref)	1.0(ref.)
≥25.0 kg/m^2	741(51.0)	713(94.9)	38(5.1)	0.76(0.49–1.19)	0.72(0.46–1.13)
p-value				0.23	0.16
Clinical tumor stage before NACT, n(%)					
cT1	394(26.8)	366(92.9)	28(7.1)	1.0(ref.)	1.0(ref.)
cT2	936(63.6)	890(95.1)	46(4.9)	0.68(0.42–1.11)	0.67(0.41–1.11)
cT3+4	142(9.6)	131(92.3)	11(7.7)	1.10(0.51–2.21)	1.30(0.58–2.78)
p-trend				0.64	0.80
Number of suspicious lymph nodes before NACT, n(%)					
1–3	1321(89.7)	1243(94.1)	78(5.9)	1.0(ref.)	1.0(ref.)
≥4	151(10.3)	144(95.4)	7(4.6)	0.77(0.32–1.60)	0.78(0.32–1.65)
p-value				0.53	0.54
Number of marked lymph nodes before NACT, n(%)					
1	1374(93.3)	1295(94.3)	79(5.7)	1.0(ref.)	1.0(ref.)
>1	98(6.7)	92(93.9)	6(6.1)	1.07(0.41–2.33)	1.29(0.48–2.87)
p-value				0.88	0.59
Histopathological tumor type, n(%)					
Ductal	1359(92.3)	1279(94.1)	80(5.9)	1.0(ref.)	1.0 (ref.)
Other	113(7.7)	108(95.6)	5(4.4)	0.74(0.26–1.69)	0.77(0.26–1.83)
p-value				0.52	0.58
Tumor subtype, n(%)					
HR+/HER2-	639(43.4)	605(94.7)	34(5.3)	1.0(ref.)	1.0(ref.)
HR+/HER2+	349(23.7)	324(92.8)	25(7.2)	1.37(0.80–2.33)	1.49(0.85–2.56)
HR-/HER2+	185(12.6)	177(95.7)	8(4.3)	0.80(0.34–1.68)	0.91(0.38–1.97)
HR-/HER2-	299(20.3)	281(94.0)	18(6.0)	1.14(0.62–2.03)	1.37(0.71–2.56)
p-value				0.53	0.42
Histological grading, n(%)					
1/2	664(45.1)	624(94.0)	40(6.0)	1.0(ref.)	1.0(ref)
3/4	808(54.9)	763(94.4)	45(5.6)	0.92(0.59–1.43)	0.94(0.59–1.51)
p-value				0.71	0.80
Type of marker, n(%)					
Clips	1132(76.9)	1053(93.0)	79(7.0)	1.0(ref.)	1.0(ref.)
Other	340(23.1)	334(98.2)	6(1.8)	**0.24(0.09–0.51)**	**0.24(0.09–0.51)**
p-value				**<0.001**	**<0.001**
Tumor multicentricity, n(%)					
No	1290(87.6)	1213(94.0)	77(6.0)	1.0(ref.)	1.0(ref.)
Yes	182(12.4)	174(95.6)	8(4.4)	0.72(0.32–1.44)	1.08(0.44–2.40)
p-value				0.39	
Clinical tumor stage after NACT, n(%)					
ycT0	642(43.6)	616(96.0)	26(4.0)	1.0(ref.)	1.0(ref.)
ycT1-4	830(46.4)	771(92.9)	59(7.1)	**1.81(1.14–2.95)**	**2.02(1.23–3.40)**
p-value				**0.01**	**0.006**
Clinical lymph node stage after NACT, n(%)					
ycN0	1209(82.1)	1141(94.4)	68(5.6)	1.0(ref.)	1.0(ref.)
ycN+	263(17.9)	246(93.5)	17(6.5)	1.16(0.65–1.96)	0.91(0.50–1.58)
p-value				0.60	0.74
Planned breast surgery, n(%)					
Breast-conserving surgery	1073(72.9)	1004(93.6)	69(6.4)	1.0(ref.)	1.0(ref.)
Mastectomy	399(27.1)	383(96.0)	16(4.0)	0.61(0.34–1.03)	**0.52(0.27–0.94)**
p-value				0.08	**0.03**
Experience in conducting TAD, n(%)					
<30	595(40.4)	552(92.8)	43(7.2)	1.0(ref.)	1.0(ref.)
≥ 30	877(59.6)	835(95.2)	42(4.8)	**0.65(0.42–1.00)**	**0.59(0.38–0.93)**
p-value				**0.05**	**0.02**

OR odds ratio; CI confidence interval; ref. reference; NACT neoadjuvant chemotherapy; HR hormone receptor; HER2 human epidermal growth factor receptor 2; TLNB target lymph node biopsy; TAD targeted axillary dissection; SLN sentinel lymph node; tln target lymph node.

CRediT authorship contribution statement

Steffi Hartmann: Conceptualization, Methodology, Writing - Original Draft, Resources, Visualization, Project administration. **Maggie Banys-Paluchowski:** Conceptualization, Methodology, Resources, Writing - Review & Editing, Project administration. **Tomasz Berger:** Conceptualization, Methodology, Writing - Review & Editing. **Nina Ditsch:** Conceptualization, Resources, Writing - Review & Editing, Project administration, Funding acquisition. **Elmar Stickeler:** Resources, Writing - Review & Editing, Project administration. **Jana de Boniface:** Conceptualization, Methodology, Resources, Writing - Review & Editing, Project administration. **Oreste Davide Gentilini:** Conceptualization, Methodology, Resources, Writing - Review & Editing, Project administration. **Jennifer Schroth:** Methodology, Formal analysis. **Guldeniz Karadeniz Cakmak:** Conceptualization, Methodology, Resources, Writing - Review & Editing, Project administration. **Isabel T. Rubio:** Resources, Writing - Review & Editing, Project administration. **Maria Luisa Gasparri:** Resources, Writing - Review & Editing, Project administration. **Michalis Kontos:** Resources, Writing - Review & Editing, Project administration. **Eduard-Alexandru Bonci:** Resources, Writing - Review & Editing, Project administration. **Laura Niinikoski:** Resources, Writing - Review & Editing, Project administration. **Dawid Murawa:** Resources, Writing - Review & Editing, Project administration. **Geeta Kadayaprath:** Resources, Writing - Review &

Table 3
Results of additional imaging due to lost axillary marker.

Patient	Type of Marker	Imaging method	Marker in situ
1	Clip	ultrasound	yes
2	Clip	CT	yes
3	Clip	CT	yes
4	Radarreflector	CT	no
5	Clip	X-ray	yes
6	Clip	ultrasound	yes
7	Clip	X-ray	yes
8	Clip	X-ray	unclear
9	Clip	X-ray	unclear
10	Clip	CT	no
11	Clip	CT	yes
12	Clip	CT + X-ray	unclear
13	Clip	mammography	yes
14	Clip	X-ray	unclear
15	Clip	CT	no
16	Clip	mammography and ultrasound	yes
17	Clip	CT	yes
18	Clip	mammography	yes
19	Clip	CT	yes
20	Clip	CT	unclear
21	Clip	CT	no
22	Clip	X-ray	yes
23	Clip	ultrasound	yes
24	Clip	CT	yes
25	Clip	X-ray	yes

CT computed tomography.

Editing, Project administration. **David Pinto:** Resources, Writing - Review & Editing, Project administration. **Florentia Peintinger:** Resources, Writing - Review & Editing, Project administration. **Ellen Schlichting:** Resources, Writing - Review & Editing, Project administration. **Lukas Dostalek:** Resources, Writing - Review & Editing, Project administration. **Helidon Nina:** Resources, Writing - Review & Editing, Project administration. **Hagitat Valiyeva:** Resources, Writing - Review & Editing, Project administration. **Marian Vanhoeij:** Resources, Writing - Review & Editing, Project administration. **Andraž Perhavec:** Resources, Writing - Review & Editing, Project administration. **Douglas Zippel:** Resources, Writing - Review & Editing, Project administration. **Lia Pamela Rebaza:** Resources, Writing - Review & Editing, Project administration. **Sarun Thongvitokomarn:** Resources, Writing - Review & Editing, Project administration. **Sarah Fröhlich:** Resources, Writing - Review & Editing. **Franziska Ruf:** Resources, Writing - Review & Editing. **Angelika Rief:** Resources, Writing - Review & Editing. **Kristina Wihlfahrt:** Resources, Writing - Review & Editing. **Timo Basali:** Resources, Writing - Review & Editing. **Marc Thill:** Resources, Writing - Review & Editing, Project administration. **Michael Patrick Lux:** Resources, Writing - Review & Editing, Project administration. **Sibylle Loibl:** Resources, Writing - Review & Editing, Supervision. **Hans-Christian Kolberg:** Resources, Writing - Review & Editing. **Jens-Uwe Blohmer:** Resources, Writing - Review & Editing. **Markus Hahn:** Resources, Writing - Review & Editing. **Meryem Gunay Gurleyik:** Resources, Writing - Review & Editing. **Mauro Porpiglia:** Resources, Writing - Review & Editing. **Semra Gunay**: Resources, Writing - Review & Editing. **Linda Zetterlund:** Resources, Writing - Review & Editing. **Thorsten Kuehn:** Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition.

Ethics statements

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

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.110253.

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