Evaluation of axillary response to neoadjuvant systemic therapy with sentinel node biopsy and axillary wire in node-positive breast cancer

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Objective: To determine the safety and reliability of directed axillary dissection with sentinel node biopsy (SNB) and marked lymph node biopsy (MLNB) with axillary wire on the clipped node, for the selection of patients who are candidates for conservative axillary treatment after the diagnosis of node-positive breast cancer who show a complete axillary response after neoadjuvant treatment. Materials: A prospective cohort study was carried out at Miguel Servet University Hospital in Zaragoza. 66 patients with a diagnosis of breast cancer and initial histological axillary involvement were finally included, in which the biopsied node was marked with a titanium clip prior to the start of neoadjuvant treatment. All patients underwent axillary sampling using SNB or Targeted axillary dissection (TAD) by SNB and MLNB with axillary wire on the clipped node before performing axillary lymphadenectomy. Results: The detection rate (DR) of the SNB was 100% with a mean of 1.8 sentinel nodes studied. In 14 patients, axillary sampling was performed only with SNB, with a false negative rate (FNR) of 14.29%, which decreased when 2 or more nodes were removed or when clipped node was removed. In 51 cases, double marking with SNB and MLNB with axillary wire was performed, which ensures excision of the clipped node in 96.1% of cases with a FNR of 1.96%. The negative predictive value (NPV) of the sample when the clipped node is studied was 96.8%. Conclusions: Targeted axillary dissection with SNB and MLNB with axillary wire on the clipped node is a safe and effective strategy for the selection of patients who are candidates for conservative axillary treatment after neoadjuvant treatment, avoiding unnecessary lymphadenectomies.

Keywords
Node-positive breast cancer, Neoadjuvant systemic therapy, Sentinel node biopsy, Axillary wire, Lymphadenectomy

1. Introduction

Neoadjuvant systemic therapy (NAST) is an increasingly widespread therapeutic strategy in the management of breast cancer, even in early stages. It provides several benefits such as early control of the disease, an assessment of the real sensitivity of the tumor, facilitating modifications or drug association in case of failure achieving a complete pathological response (pCR), and it allows the performance of conservative surgery in a percentage of tumors that would otherwise require a more mutilating surgery [1, 2].

The complete pathological axillary response rate ranges between 13% and 60% according to published series and it depends on the tumor subtype. The Human Epidermal Growth Factor Receptor 2 (HER2)-positive and hormonal receptor negative subtype was associated with the highest axillary pCR rate (60%) [3, 4].

Axillary lymphadenectomy (ALND) is considered the gold standard of surgical treatment in patients with node-positive breast cancer at the time of diagnosis (pN1+). However, in cases of pathological complete response to NAST, the benefit of lymphadenectomy seems to be lower than the morbidity and the loss in quality of life associated with this procedure [3–6].

The publication of the After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) and American College of Surgeons Oncology Group (ACOSOG) Z0011 studies, which showed no differences in the axillary recurrence and overall survival rates in patients with positive sentinel nodes in whom complete lymph node dissection was omitted, increases the interest in promoting conservative management in responders to NAST [1, 4]. Although residual axillary disease after NAST could have different prognostic implications, the response results are optimistic taking into account the biology of the tumor. However, it is essential to obtain survival data in patients treated with NAST and conservative axillary surgery in the long term [2, 4].

Lymph node preservation requires the establishment of reliable and safe protocols for the selection of patients for surgical de-escalation in order not to worsen the prognosis of their disease. The clinical or radiological examination does not have sufficient sensitivity or specificity to rule out residual disease [5, 7].
Sentinel node biopsy (SNB) is established as the axillary staging method in patients with initial negative node involvement, even in cases treated with NAST. In this context, the detection rate (DR) is greater than 96%, the false negative rates (FNR) are around 5% and the axillary recurrence rate is less than 1.2% [7].

In the different studies that propose the use of SNB for axillary sampling after NAST in pN1+ patients, the series are heterogeneous, with detection rates between 80–92% and FNR higher than 10%, involving the extraction of a large number of sentinel lymph nodes to improve it [8].

Targeted axillary dissection (TAD) seems to be the best sampling option, even over marked lymph node biopsy (MLNB) [8]. TAD aims to assess the axillary state after NAST through SNB associated with MLNB, marking the affected lymph node at the time of biopsy using a radio-opaque clip, a ferromagnetic seed, radioiodine or carbon tattooing [8, 9].

In this work, the experience of our center in axillary sampling in patients with node-positive breast cancer who are treated with NAST is collected. The aim is to determine the safety and reliability of the procedure by showing the detection rate (DR), false negative rate (FNR) and negative predictive value (NPV) in this setting using TAD by SNB and MLNB with axillary wire on the clipped node against only SNB.

2. Materials and methods

2.1 Design of the study

A prospective cohort study was carried out by the Breast Pathology Unit of the Miguel Servet University Hospital from May 2018 to January 2021. All patients were duly informed of the objectives and procedure of the study and they were required to sign a written informed consent for their inclusion. Patients were included in the study once the diagnosis was confirmed and data collection was completed once the systemic and locorregional treatment had been completed.

2.2 Study population and management protocol

The study enrolled 74 patients with initial node-positive breast cancer, in which the axillary involvement by the tumor was confirmed histologically by core needle biopsy and the biopsied node was marked with a titanium clip prior to the start of neoadjuvant therapy. The marker used is a ribbon shape of UltraClip™ (Bard Peripheral Vascular Inc, Tempe, AZ, USA.) Dual Trigger Breast Tissue Marker-17 G x 12 cm.

Tumor size or the presence of multifocality or multicentricity were not considered among the selection criteria as they are managed independently in breast cancer [7–10].

Cases of non-migration of the nanocolloid without associated wire, initial axillary involvement of II or III Berg levels, patients who did not complete the planned treatment scheme and those with disease in progression or without response to NAST were excluded, so finally 66 patients were included in the analysis.

2.2.1 Neoadjuvant Systemic Therapy (NAST)

Systemic therapy regimens were determined according to the characteristics of each patient and their tumor. However, these were adapted to the current clinical protocols and guidelines in all cases. Both neoadjuvant chemotherapy (CT) and endocrine therapy (ET) with aromatase inhibitors were eligible treatments. The average treatment time was 6 months.

Standard CT regimens contained anthracyclines and taxanes. In Her2-positive disease, CT was combined with Her2 targeted therapy.

2.2.2 Axillary response evaluation

Clinical and radiological response was evaluated by comparing ultrasound findings in axillary lymph nodes at diagnosis with those after the end of NAST before performing surgery.

The radiological response was classified according to the criteria of the Union for International Cancer Control (UICC) [11] as complete axillary response, with disappearance of lesions, mayor partial response, with reduction in tumor size of 50% or greater, minor partial response, with reduction of less than 50% and no response without changes of size tumor.

The pathological response was assessed with the analysis of the lymph nodes removed as axillary sampling and those obtained with the subsequent complete lymphadenectomy. A paraffin-fixed hematoxylin-eosin stain was used and the pathological response was classified according to the Miller & Payne system: N-A (negative lymph nodes, no changes attributable to CT), N-B (positive lymph nodes, no changes attributable to CT), N-C (positive lymph nodes, but with evidence of partial response), N-D (negative lymph nodes, with changes attributable to CT) [11, 12].

Based on this analysis, post-treatment axillary status is classified once the tumor nodes metastases had been treated with (yTNM) system of the 8th edition of the American Joint Committee on Cancer (AJCC) staging system: yN0 or complete axillary pathological response, yN0 (i+mol+) or lymph nodes with isolated tumor cells after CT, which is not considered complete response, yN1mi or presence of micrometastases (metastasis size between 0.2 and 2 mm) and yN1 or presence of metastases greater than 2 mm [11].

2.2.3 Lymphatic mapping technique

Intraoperative lymph node sampling with SNB was proposed until March 2019. SNB was performed by a single-tracer method (99mTc) the day before surgery and followed by perioperative use of gamma probe. Subsequently, the protocol was adapted by adding a second axillary mapping system, MLNB. Therefore, since March 2019, TAD with SNB and MLNB with axillary wire on the clipped node was performed, ensuring the excision and the histological analysis of the initially affected lymph node, which not always coincide with the sentinel node [7–9]. In all cases, a complete axil-
74 Patients with Node Positive Breast Cancer and Neoadjuvant Systemic Therapy

66 Patients with Node Positive Breast Cancer and Neoadjuvant Systemic Therapy

51 SNB + MLNB Wire
14 SNB
1 MLNB Wire

**Fig. 1.** Study population and application of selection criteria.

lary lymphadenectomy was performed, as it was established by the protocol in force in our center.

### 2.3 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics v25 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean and standard deviation, whereas categorical variables were expressed as percentages. Categorical variables were compared with a χ² test or Fisher’s exact test, and a Student’s t-test was used to compare the continuous variables. Statistical significance was defined as p < 0.05.

Besides, detection rate (DR), false negative rate (FNR) and negative predictive value (NPV) of the TAD by using SNB and axillary wire on the clipped node against only SNB, were calculated.

### 3. Results

A total of 74 patients were recruited, of which 8 were excluded, 4 due to non-migration of the nanocolloid without associated wire, one due to not completing treatment, and three due to massive axillary disease (Fig. 1).

The sample of 66 patients has a mean age of 59 years, with a 63.6% of postmenopausal women. The mean tumor size by Magnetic Resonance Imaging (MRI) is 31 mm with 50% of cases of multifocality. The most frequent histological subtype is Her2-positive (18.2% with negative HR and 21.2% with positive HR), followed by Luminal B (36.4%). Triple-negative breast cancers account for 13.6%. 77% of the tumors have a high Ki67 above 20%, lymphovascular invasion is observed in 33.3% of the cases and 86.4% are treated with a CT regimen (Table 1).

The group of SNB, as the only axillary mapping technique, is made up of 14 patients (21.2%) compared to 51 cases of double mapping (SNB + MLNB with axillary wire). There is a single wire case. The sentinel node (SN) detection rate is 100% as long as the proper migration of the nanocolloid occurs. The mean number of SNs extracted is 1.8 (Table 2).

The SN coincides with the clipped node, without taking into account the sampling technique, in 74.2% of the patients (Table 2). When we only used the SNB, we obtained the clipped node in 78.6% of the cases. However, if the axillary wire is added, we extract the clipped node in 96.1% (Table 3).

The rate of residual axillary involvement after NAST in the sample is 53%. Of these, only in three cases the axillary sampling was negative, that is, the general FNR of the axillary sampling is 4.5% (Table 4). The mean of nodes obtained for sampling is 2.18 in the entire series (Table 2).

If the axillary sampling with only SNB subgroup is analyzed, the FNR is 14.29%, which drops to 0% if two or more sentinel nodes are removed (Table 4).

If the clipped node is included in the sample (MLNB), the FNR drops to 1.6%, compared to 40% of false negatives if we do not study the clipped node, with a statistically significant difference. In this way, by adding the double mapping technique with SNB + MLNB with wire that ensures the excision of the clipped node in 96.1% of cases (Table 3), the FNR of the sampling drops to 1.96% (Table 4).

In the sample of the present study, the NPV regarding the existence of residual axillary disease after NAST in lymphadenectomy after a negative sampling is 91.2%. When analyzing the cohort in which the clipped node was extracted using a wire, the NPV was 96.8%, while in the cohort in which the clipped node was not analyzed, the NPV was 33.3% (Table 5).

Predictors of complete axillary response with statistical significance include the HER2 positive tumor subtype and the
Breast cancer is the most common neoplasm among women, with an overall incidence of 12%. Early stage survival ranges from 73% to 91% at 5 years, so this implies the need to offer therapies with few side effects and with the least possible impact on their quality of life [2, 13].

Lymphedema is a side effect associated with lymph node excision. Its frequency of appearance and its severity depends on the number and the levels of lymph nodes that are removed, and the association with axillary RT. Besides, there are individual factors of each anatomy or related to lifestyle habits that influence the development of this complication. Rockson’s series show rates of 14–18%, decreasing since axillary RT fields are optimized [14].

There is great variability in clinical guidelines regarding axillary management in node-positive patients (pN+) who respond to NAST (cyN0). European Society for Medical Oncology (ESMO) [15] and National Comprehensive Cancer Network (NCCN) [16] contemplate the use of SNB in pN+ patients after NAST, advising the double marking system on the biopsied node (TAD) or the extraction of at least 3 sentinel nodes in ESMO and 2 or more in the case of NCCN. American Society Breast Surgeons [17] recommends SNB with double tracer, completing ALND if two sentinels or clipped node are not removed. The Swedish [18] or Finnish [19] guides bet on direct ALND. Denmark guide [20] and Germany guide (AGO Committee) [21] advocates for TAD. In the case of the Spanish Oncology Society (SEOM) [22], a direct ALND is indicated except in cases where two negative lymph nodes are removed and one of them is the clipped one.

It is essential to agree on a safe system for the selection of patients for conservative axillary management that discriminates patients with residual disease susceptible to more aggressive surgeries and adjuvant therapies, such as Her2 and triple negative tumors [8, 23].

The assessment of the tumor response to NAST allows establishing response predictive factors that facilitate a first selection of patients.

According to the published literature, in our sample, the Her2-dependent tumor subtypes, those with the highest histological grade and with the highest proliferative capacity, are the ones that make the best responses to systemic treatment. In this study, the group of triple negatives likes tumors is small to present significant differences despite being classified as a good responder group [4, 24, 25].

In our center, the radiological capacity to rule out residual axillary disease is very high, with evaluations of complete response in 65.1% of patients who do not finally present subsequent histological alteration. However, this measure is not enough to justify a conservative management since it is an operator–dependent technique and therefore, it is not reproducible [11].

As suggested by the initial working groups of ACOSOG Z1071 [23], Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SN FNAC) [26], SENTinel NeoAdjuvant (SENTINA) [27] and Ganglion sentinel apres chimiotherapie NEOAdjuvante (GANEAT) [28], a reliable axillary assessment system is required with FNR less than 10% and high NPV that allows decision-making. In these trials, the pathological study is performed using SNB with a double mapping system, radiotracer and stain (blue day), which allows

| Table 1. Descriptive analysis. |
|-----------------------------|
| N = 66 cases                |
| Age                        |
| Menopause                   |
| - Premenopausal             |
| - Postmenopausal            |
| Tumor size in MRI           |
| Histological grade          |
| - G1–G2                    |
| - G3                       |
| Lymphovascular invasion     |
| - No                       |
| - Yes                      |
| Tumor subtype               |
| - Luminal A like            |
| - Luminal B like            |
| - HER2+                     |
| - Triple-negative like      |
| - Luminal B + HER2+         |
| Ki67                        |
| - <20%                      |
| - >20%                      |
| Neoadjuvant systemic therapy|
| - Chemotherapy              |
| - Hormonotherapy            |
| Axillary response in Radiological Study |
| - No response               |
| - Minor partial reduction (<30%) |
| - Complete response (>90%)  |

**a** Data expressed as mean and standard deviation; **b** Data expressed as percentages N (%).

MRI, Magnetic Resonance Imaging; G1, Grade 1; HER2, Human Epidermal Growth Factor Receptor 2.
Table 2. Descriptive analysis.

| Description                                              | N = 66 cases |
|----------------------------------------------------------|--------------|
| **Axillary mapping technique**                           |              |
| - SNB                                                    | 14 (21.2%)   |
| - MLNB wire                                              | 1 (1.5%)     |
| - SNB + MLNB wire                                        | 51 (77.3%)   |
| **Sentinel node affection**                              |              |
| - No                                                     | 38 (57.6%)   |
| - Yes                                                    | 28 (42.4%)   |
| **Sentinel node coincides with the clipped node**        |              |
| - No                                                     | 12 (18.2%)   |
| - Yes                                                    | 49 (74.2%)   |
| - Not applicable                                         | 5 (7.6%)     |
| **Clipped node obtained in the sampling**                |              |
| - No                                                     | 5 (7.6%)     |
| - Yes                                                    | 61 (92.4%)   |
| **Number of nodes obtained in the sampling**             |              |
| - 1 node                                                 | 25 (37.9%)   |
| - 2 nodes                                                | 19 (28.8%)   |
| - ≥ 3 nodes                                              | 22 (33.3%)   |
| **Residual axillary involvement after NAST**             |              |
| - No                                                     | 31 (47%)     |
| - Yes                                                    | 35 (53%)     |
| **Residual axillary involvement after NAST in ALND**     |              |
| - No                                                     | 55 (83.3%)   |
| - Yes                                                    | 11 (16.7%)   |
| **Residual axillary involvement after NAST in ALND with negative sampling** |              |
| - No                                                     | 31 (47%)     |
| - Yes                                                    | 3 (4.5%)     |
| - Positive sampling                                      | 32 (48.5%)   |

* Data expressed as mean (standard deviation); † Data expressed as percentages N (%).

Abbreviations: SNB, Sentinel Node Biopsy; MLNB, Marked Lymph Node Biopsy; NAST, Neoadjuvant Systemic Therapy; ALND, Axillary lymphadenectomy.

The extraction of a greater number of lymph nodes as a strategy to reduce FNR. The detection rate is between 80–92% [23, 26, 27]. In our center, injection with Tc99 allows us to locate the sentinel node (SN) in 100% of cases, although the number of SNs extracted is low, with a mean of 1.8. In previous studies, it is clear that the number of SLN necessary to achieve assumable FNR is two or higher in the case of SN FNAC [26] or three in the rest [23, 27], with FNR of 24% with only one SN, which decreases to 5–6% with two or higher. In our series, the FNR with a single SN is 12%, which reduces to below 5% if two or more nodes are removed or in cases in which the SN coincides with the clipped node.

Secondary fibrosis and blockage of the lymphatic pathways after NAST changes drainage at the axillary level, which means that in one of every four cases the SN does not correspond to the clipped node [7–10]. In our registry, 78.57% of SNs coincide with the node marked with the clip.
Table 4. False negative rates of the axillary marking methods.

| Residual axillary involvement after NAST in ALND with negative sampling | No (%) | Yes (%) | \( \rho \) | OR (95% CI) |
|---|---|---|---|---|
| Axillary mapping technique | 63 (95.5%) | 3 (4.5%) | | |
| - MLNB wire | 1 (100%) | - | | |
| - SNB | 12 (85.71%) | 2 (14.29%) | - | - |
| - SNB + MLNB wire | 50 (98.04%) | 1 (1.96%) | | |
| Targeted axillary dissection | 13 (86.7%) | 2 (13.3%) | 0.127 | - |
| - No | 50 (98.04%) | 1 (1.96%) | | |
| Clipped node obtained | 3 (60%) | 2 (40%) | 0.014 | 0.025 (0.002–0.360) |
| - No | 60 (98.4%) | 1 (1.6%) | | |
| Number of nodes in sampling | | | | |
| - 1 node | 22 (80%) | 3 (12%) | 0.050 | - |
| - 2 nodes | 19 (100%) | - | | |
| - ≥3 nodes | 22 (100%) | - | | |

* Bold entries mean that the \( p \)-value was <0.05, which is statistically significant.

Abbreviations: SNB, Sentinel Node Biopsy; MLNB, Marked Lymph Node Biopsy NAST, Neoadjuvant Systemic Therapy, ALND, Axillary lymphadenectomy.

Table 5. Negative Predictive Values of the sample.

| Residual axillary involvement after NAST in ALND | No (%) | Yes (%) | \( \rho \) | OR (95% CI) |
|---|---|---|---|---|
| Sampling | 55 (83.3%) | 11 (16.7%) | | |
| - Negative sampling | 31 (91.2%) | 3 (8.8%) | 0.104 | - |
| - Positive sampling | 24 (75%) | 8 (25%) | | |
| Clipped node obtained (61 cases) | | | | |
| - Negative sampling | 30 (96.8%) | 1 (3.2%) | 0.026 | 9.1 (1.05–79.5) |
| - Positive sampling | 23 (76.7%) | 7 (23.3%) | | |
| No clipped node obtained (5 cases) | | | | |
| - Negative sampling | 1 (33.3%) | 2 (66.7%) | 1 | - |
| - Positive sampling | 1 (50%) | 1 (50%) | | |

* Bold entries mean that the \( p \)-value was <0.05, which is statistically significant.

Abbreviations: NAST, Neoadjuvant Systemic Therapy; ALND, Axillary lymphadenectomy.

The results of the prospective German multicenter registry study (SenTa) presented at the ESMO conference in 2019 [29, 30] with 473 patients, show the convenience of ensuring excision and evaluation of the initial positive node. For this, it is necessary to carry out a marking of the node at the time of the biopsy in order to recover it during the surgery. There is no consensus regarding the marking system. Most of the published data refer to the clip (titanium, propylene, etc.), although there are clear benefits of marking with seeds (radioactive, ferromagnetic or by radar signal) that can be placed prior to NT and do not require the use of a pre-surgical locator system [1, 10, 21].

In a meta-analysis of more than 3000 patients, targeted axillary dissection (TAD), that is, the association of SNB with marked lymph node biopsy (MLNB), is presented as the safest method of axillary sampling with a DR of 90% (95% CI: 85.1–95.1) and a FNR of 5.18% (95% CI: 3.41–7.54) [8].

In our sample, TAD was performed with SNB-Tc99 associated with the excision of a node marked with a wire on a HidroMark clip. The FNR was 1.96% regardless of the number of lymph nodes removed. The NPV was 96.77% provided the clipped node was analyzed. The DR of clipped node was 96.1% when the axillary wire was added. These data support the sensitivity of this patient selection system for decision-making.
Table 6. Predictors of complete axillary response to neoadjuvant systemic therapy.

| Residual Axillary Involvement | No | Yes | \(\beta\) | OR (95% CI) |
|------------------------------|----|-----|----------|-------------|
| Age \(^a\)                   | 31 (47%) \(^b\) | 35 (53%) \(^b\) | 0.748 | - |
| Tumor size in MRI \(^a\)    | 34.97 (16,038) | 28.17 (11,224) | **0.048** | - |
| Multifocality \(^b\)        |    |     |          |             |
| - No                        | 18 (56.3%) | 14 (43.7%) | 0.143 | - |
| - Yes                       | 13 (38.2%) | 21 (61.8%) |          |             |
| Ki67 \(^b\)                |    |     |          |             |
| - <20%                      | 3 (20%) | 12 (80%) | **0.017** | **0.205 (0.052–0.816)** |
| - >20%                      | 28 (54.9%) | 23 (45.1%) |          |             |
| Histological Grade \(^b\)  |    |     |          |             |
| - G1–G2                     | 16 (33.3%) | 32 (66.7%) | <**0.001** | **0.1 (0.025–0.396)** |
| - G3                        | 15 (83.3%) | 3 (16.7%) |          |             |
| Lymphovascular invasion \(^b\) |    |     |          |             |
| - No                        | 17 (38.6%) | 27 (61.4%) | 0.055 | - |
| - Yes                       | 14 (63.6%) | 8 (36.4%) |          |             |
| Tumor Subtype \(^b\)       |    |     |          |             |
| - Luminal A like            | 1 (14.3%) | 6 (85.7%) | 0.11 | - |
| - Luminal B like            | 4 (16.7%) | 20 (83.3%) | <**0.001** | **9.0 (2.591–31.266)** |
| - HER2+                     | 10 (83.3%) | 2 (16.7%) | **0.005** | **0.127 (0.025–0.639)** |
| - Triple-Negative like      | 6 (66.7%) | 3 (33.3%) | 0.287 | - |
| - Luminal B + HER2+         | 10 (71.4%) | 4 (28.6%) | **0.039** | **0.271 (0.075–0.98)** |
| Neoadjuvant systemic therapy \(^b\) |    |     |          |             |
| - CT                        | 31 (54.4%) | 26 (45.6%) | 0.149 | - |
| - HT                        | 2 (22.2%) | 7 (77.8%) |          |             |
| Axillary response RX \(^b\) |    |     |          |             |
| - No complete response      | 3 (13%) | 20 (87%) | <**0.001** | **0.08 (0.021–0.315)** |
| - Complete response (>90%) | 28 (65.1%) | 15 (34.9%) |          |             |

\(^a\) Data expressed as mean (standard deviation); \(^b\) Data expressed as percentages N (%).

**Bold entries** mean that the \(\beta\)-value was < 0.05, which is statistically significant.

CT, Chemotherapy; HT, Hormone Therapy.

Most of the cases of failure in the placement of the wire or non-migration of the tracer are found in the group of patients excluded due to massive axillary disease or non-response to treatment.

The follow-up data regarding disease recurrence and overall survival will probably encourage consensus. The European Breast Cancer Research Association of Surgical Triallists (EUBREAST) has begun recruitment for a prospective multinational cohort study, AXSANA (Axillary surgery after neoadjuvant treatment) (NCT04373655), which enrolls cN+ patients undergoing neoadjuvant chemotherapy (NACT) who convert to ycN0. The aim of AXSANA is to assess the impact of different surgical staging procedures in the axilla on the oncologic outcome and on health-related quality of life [30].

The present study is limited by the number of cases collected, which does not allow obtaining significant differences regarding predictive factors. Besides, it will be necessary to continue recruiting cases and monitoring patients in order to obtain our own local and distant recurrence rates.

5. Conclusions

Targeted axillary dissection with SNB plus axillary wire on the clipped node is a safe and reliable strategy for the selection of patients who are candidates for conservative axillary treatment after neoadjuvant treatment, avoiding unnecessary lymphadenectomies in patients that respond to neoadjuvant systemic therapy.

**Author contributions**

JNS and PRC performed the review of the literature. PRC, FJVS and IVG performed the axillary and breast surgeries. MCGM carried out the breast and axillary imaging study and she placed the wire on the clipped node. JNS and AER carried out the statistical analysis. JNS and PRC wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.
Ethics approval and consent to participate
All patients were required to sign a written informed consent for their inclusion in this study. The publication of this original research was approved by Aragon Ethics Committee (CEICA), in act number 06/2016, in Zaragoza, Spain. Besides, this work complied with the declaration of Helsinki for Human Research of 1974 (last modified in 2000).

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Conflict of interest
The authors declare no conflict of interest.

References
[1] Donker M, Straver ME, Wesseling J, Loo CE, Schot M, Drukker CA, et al. Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. Annals of Surgery. 2015;261: 378–382.

[2] Early Breast Cancer Trials’ Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncology. 2018; 19: 27–39.

[3] Kim WH, Kim HJ, Park HY, Park JY, Chae YS, Lee SM, et al. Axillary Pathologic Complete Response to Neoadjuvant Chemotherapy in Clinically Node-Positive Breast Cancer Patients: a Predictive Model Integrating the Imaging Characteristics of Ultrasound Restaging with Known Clinicopathologic Characteristics. Ultrasound in Medicine & Biology. 2019; 45: 702–709.

[4] Samiei S, Simons JM, Engelen SME, Beets-Tan RGH, Classe JMJ, Smidt ML. Axillary pathologic complete response after neoadjuvant systemic therapy by breast cancer subtype in patients with initially clinically node-positive disease: a systematic review and meta-analysis. JAMA Surgery. 2021; 156: e210891.

[5] Charalampoudis P, Markopoulos C, Kovacs T. Controversies and recommendations regarding sentinel lymph node biopsy in primary breast cancer: a comprehensive review of current data. European Journal of Surgical Oncology. 2018; 44: 5–14.

[6] Kuru B. The adventure of axillary treatment in early stage breast cancer. European Journal of Breast Health 2020; 16: 1–15.

[7] Wazir U, Mobkel K. De-escalation of Axillary Surgery in the Neoadjuvant Chemotherapy (NACT) Setting for Breast Cancer: is it Oncologically Safe? Anticancer Research. 2020; 40: 5351–5354.

[8] Swarnkar PK, Tayeh S, Michell MJ, Mobkel K. The evolving role of marked lymph node biopsy (MLNB) and targeted axillary dissection (TAD) after neoadjuvant chemotherapy (NACT) for node-positive breast cancer: systematic review and pooled analysis. Cancers. 2021; 13: 1539.

[9] Li Y, Zhou Y, Mao F, Lin Y, Zhang X, Shen S, et al. The diagnostic performance of minimally invasive biopsy in predicting breast pathologic complete response after neoadjuvant systemic therapy in breast cancer: a meta-analysis. Frontiers in Oncology 2020; 10: 933.

[10] Simons JM, van Nijatten TJA, van der Pol CC, Luiten EJT, Koppert LB, Smidt ML. Diagnostic Accuracy of Different Surgical Procedures for Axillary Staging after Neoadjuvant Systemic Therapy in Node-positive Breast Cancer. Annals of Surgery. 2019; 269: 432–442.

[11] Bossuyt V, Provenzano E, Symmans WF, Boughey JC, Coles C, Carugliano G, et al. Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration. Annals of Oncology. 2015; 26: 1280–1291.

[12] Tadros AB, Yang WT, Krishnamurthy S, Rauch GM, Smith BD, Valero V, et al. Identification of Patients with Documented Pathologic Complete Response in the Breast after Neoadjuvant Chemotherapy for Omission of Axillary Surgery. JAMA Surgery. 2017; 152: 665–670.

[13] Zetterlund LH, Frisell J, Zouzos A, Axelsson R, Hatschek T, de Boniface J, et al. Swedish prospective multicenter trial evaluating sentinel lymph node biopsy after neoadjuvant systemic therapy in clinically node-positive breast cancer. Breast Cancer Research and Treatment. 2017; 163: 103–110.

[14] Rockson SG. Lymphedema after Breast Cancer Treatment. New England Journal of Medicine. 2018; 579: 1937–1944.

[15] Cardoso F, Kyriakides S, Ohno S, Penttula-Liorca F, Poormants P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2019; 30: 1674.

[16] NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, Version 1.2021–15 January 2021. NCCN.org. 2021. Available at: https://www.nccn.org/professionals/physician_gls/fdccaﬄt.aspx#breast (Accessed: 27 March 2021).

[17] Consensus Guideline on the Management of the Axilla in Patients with Invasive/In-Situ Breast Cancer. The American Society of Breast Surgeons. 2019. Available at: https://www.breastsurgeons.org/docs/statements/Consensus-G uideline-on-the-Management-of-the-Axilla.pdfv2 (Accessed: 27 March 2021).

[18] Regional cancercentrum i samverkan. Bröstcancer-Nationell Vårdprogram-SweBCG, 2020. Available at: http://www.swebcg.se/wp-content/uploads/2020/10/nati onell-vardprogram-brostcancer_202011.pdf (Accessed: 1 December 2020).

[19] Finnish Breast Cancer Group. Rintasyöpäryhmän Valtakunnallinen Diagnostiikka—Ja Hoitosuositus. 2019. Available at: https://1587667.167.directo.fi/@Bin/c554c241df494d864925e07ad6aa705e/1614023914/application/pdf/186425/SRSR_Suosi tus_2019%20jouluku.pdf (Accessed: 1 December 2019).

[20] Halberg AK, Gravesen CD, Cold S, Jensen JD. Neoadjuvant chemotherapy for primary operable breast cancer. Danish Medical Journal. 2020; 67: A0120010.

[21] Recommendations of the AGO Breast Committee: Diagnosis and Treatment of Patients with early and advanced Breast Cancer. 2018. Available at: www.ago-online.de (Accessed: 27 March 2021).

[22] Ayala de la Peña F, Andrés R, García-Sáenz JA, Manso L, Margelli M, Dalmau E, et al. SEOM clinical guidelines in early stage breast cancer (2018). Clinical and Translational Oncology. 2019; 21: 18–30.

[23] Boughhey JC, Ballman KV, Le-Petross HT, McCall LM, Mittendorf EA, Ahrendt GM, et al. Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting with Node-positive Breast Cancer (T0-T4, N1-N2) who Receive Neoadjuvant Chemotherapy: Results from ACOSOG Z1071 (Alliance) Annals of Surgery. 2016; 263: 802–807.

[24] Denkert C, von Minckwitz G, Darb-Esfahani S, Lederer B, Hepner BI, Weber KE, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncology. 2018; 19: 40–50.

[25] O’Halloran N, Lowery A, Curran C, McLaughlin R, Malone C, Sweeney K, et al. A Review of the Impact of Neoadjuvant Chemotherapy on Breast Surgery Practice and Outcomes. Clinical Breast Cancer. 2019; 19: 377–382.
Boileau J, Poirier B, Basik M, Holloway CMB, Gaboury L, Sideris L, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. Journal of Clinical Oncology. 2015; 33: 258–264.

Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncology. 2013; 14: 609–618.

Classe J, Loaec C, Gimbergues P, Alran S, de Lara CT, Dupre PF, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Research and Treatment. 2019; 173: 343–352.

Kuemmel S, Heil J, Rueland A, Seiberling C, Harrach H, Schindowski D, et al. A Prospective, Multicenter Registry Study to Evaluate the Clinical Feasibility of Targeted Axillary Dissection (TAD) in Node-Positive Breast Cancer Patients. Annals of Surgery. 2020. (in press)

Banys-Paluchowski M, Gasparri ML, de Boniface J, Gentilini O, Stickeler E, Hartmann S, et al. The Axsana Study Group. Surgical Management of the Axilla in Clinically Node-Positive Breast Cancer Patients Converting to Clinical Node Negativity through Neoadjuvant Chemotherapy: Current Status, Knowledge Gaps, and Rationale for the EUBREAST-03 AXSANA Study. Cancers. 2021; 13: 1565.