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Technical feasibility and safety of hooked wire localisation for targeted axillary dissection after neoadjuvant chemotherapy in patients with node-positive breast cancer.

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ABSTRACT

Background: Targeted axillary dissection (TAD) has been proposed as an alternative method for axillary staging node negative patients after neoadjuvant chemotherapy treatment (NACT). TAD combines the sentinel lymph node biopsy (SLNB) as well as the removal of the node-positive marked nodes at diagnosis.

Aim: To determine the technical feasibility and safety of our TAD technique and to describe the oncological results and axillary recurrence, so as this can provide more information regarding which patients may benefit from this less invasive axillary staging.

Methods: A single-centre prospective study from 2019 to 2023 including patients with axillary disease and ycN0 post NACT that underwent TAD. Before systemic treatment, a clip was placed in those proven metastasis nodes. TAD with hooked wire guided excision of the clipped node and SLNB with double tracer were performed. If axillary disease was found or there was technical failure, axillary lymph node dissection (ALND) was performed.

Results: Clip marking procedure pre NACT as well as the placement of the hooked wire were performed successfully. TAD was completed in 19 patients (79.2%) and the clipped node identification rate (IR) was 91.6%. On 14 patients (74.83%) the clipped node coincided as a sentinel node (SLN). There were 10 patients (41.6%) who only required TAD, while 14 (58.3%) also required ALND.

Conclusion: TAD with clipped node at diagnosis and subsequent localization using a hooked wire is a feasible and safe technique that can allow avoiding ALND in selected patients. Marking the positive nodes at diagnosis provides greater oncological safety.

Resumen: *La disección axilar dirigida (TAD) se ha propuesto como un método alternativo para la estadificación axilar en los pacientes con ganglios negativos después del tratamiento con quimioterapia neoadyuvante (NACT). TAD combina la biopsia del ganglio linfático centinela (SLNB) así como la extirpación de los ganglios marcados como positivos en el momento del diagnóstico.*

Objetivos: *Determinar la viabilidad técnica y la seguridad de nuestra técnica TAD y describir los resultados oncológicos y la recidiva axilar, de forma que pueda aportar más información sobre qué pacientes pueden beneficiarse de esta estadificación axilar menos invasiva.*

Métodos: *Estudio prospectivo unicéntrico que incluye las pacientes atendidas entre 2019 y 2023 con enfermedad axilar y ycN0 post NACT que fueron sometidas a TAD. Antes del tratamiento sistémico, se colocó un clip en aquellos ganglios positivos confirmados. Se realizó TAD con extirpación guiada con*

arpón del ganglio clipado y SLNB con doble trazador. Si se encontraba enfermedad axilar o se producía fallo de técnica, se realizaba linfadenectomía axilar (ALND).

Resultados: *El marcaje con clips pre NACT así como la colocación del arpón se realizaron con éxito. La TAD se completó en 19 pacientes (79.2 %) y la tasa de identificación de los ganglios clipados (IR) fue del 91.6 %. En 14 pacientes (74.83%) el ganglio clipado coincidió como ganglio centinela (GC). Hubo 10 pacientes (41.6%) que solo requirieron TAD, mientras que 14 (58.3%) también requirieron ALND.*

Conclusiones: *La TAD con ganglio clipado en el momento del diagnóstico y su posterior localización mediante arpón es una técnica fiable y segura que puede permitir evitar la ALND en pacientes seleccionados. Marcar los ganglios positivos al diagnóstico proporciona una mayor seguridad oncológica.*

Resum: *La dissecció axil·lar dirigida (TAD) s'ha proposat com un mètode alternatiu per a l'estadificació axil·lar dels pacients amb ganglis negatius després del tractament amb quimioteràpia neoadyuvante (NACT). TAD combina la biòpsia del ganglio limfàtic sentinella (SLNB) així com l'extirpació dels ganglis marcats com positius en el moment del diagnòstic.*

Objectius: *Determinar la viabilitat tècnica i la seguretat de la nostra tècnica TAD i descriure els resultats oncològics així com la recidiva axil·lar, de forma que pugui aportar més informació sobre quins pacients poden beneficiar-se d'aquesta estadificació axil·lar menys invasiva.*

Mètodes: *Estudi prospectiu unicèntric que inclou les pacients ateses entre 2019 i 2023 amb malaltia axil·lar i ycNO post NACT que es van sotmetre a TAD. Abans del tractament sistèmic, es va col·locar un clip en aquells ganglis positius comprovats. Es va realitzar TAD amb extirpació guiada amb arpó del ganglio clipat i SLNB amb doble traçador. Si es trobava malaltia axil·lar o hi havia fallada de tècnica, es realitzava linfadenectomía axil·lar (ALND).*

Resultats: *El marcatge amb clips pre NACT així com la col·locació de l'arpó es van realitzar amb èxit. La TAD es va completar en 19 pacients (79.2 %) i la taxa d'identificació del gangli clipat (IR) va ser del 91.6 %. En 14 pacients (74.833%) el ganglio clipat va coincidir com a ganglio sentinella (GS). Va haver-hi 10 pacients (41,6%) que només van requerir TAD, mentre que 14 (58.3%) també van requerir ALND.*

Conclusiones: *La TAD amb gangli clipat en el moment del diagnòstic i la seva posterior localització mitjançant arpó és una tècnica fiable i segura que pot permetre evitar la ALND en pacients seleccionats. Marcar els ganglis positius al diagnòstic proporciona una major seguretat oncològica.*

INTRODUCTION

Currently, breast cancer has overtaken lung cancer as the most frequent in the world ^[1]. One of the most important prognostic factor in breast cancer, both diagnostically and therapeutically, is the axillary lymph node status ^[2].

Axillary disease guides some important decisions like the requirement of systemic treatment or the extension of the surgical procedure. Sentinel lymph node biopsy (SLNB) is the standard procedure for patients with node negative axilla (N0). This technique has shown not to compromise the global survival, the free disease survival or the locoregional control in this group of patients ^[3]. Therefore, SLNB in those patients has the capacity to reflect in an efficient and safety way the status of the residual axillary nodes ^[3-6]. On the contrary, axillary lymph node dissection (ALND) is the standard procedure in clinically node-positive patients. However, this technique is associated with significant morbidity and an important decrease of life quality ^[7]. Its most feared adverse effect is lymphedema, which has a range of appearance from 6.7% to 62.5%, being the extension of the axillary procedure a determinant risk factor ^[8]. Other important adverse effects are pain, reduced mobility of the arm, paraesthesia and numbness. In consequence, the research for new less invasive techniques for the management of axillary disease is under discussion.

Recent studies focus on those patients initially presenting node-positive disease that have a pathological complete response (ypN0) in the axilla after neoadjuvant chemotherapy treatment (NACT). Although ALND still remains the standard of care in most guidelines post NACT ^[9], disagreements between experts have been increasing. One of the reasons for this discordance is due to the demonstration that in 40-75% of cases NACT can eradicate the axillary proven metastasis ^[10-12]. Furthermore, other studies corroborate the uncertain and limited role that ALND may play after effective NACT in the prevention of recurrence as well as in the improvement of survival of ypN0 patients ^[13-14]. Consequently, research is focusing on the de-escalation of surgical staging procedures.

SLNB has been one of the methods evaluated in these patients with pathological complete response to NACT in the previous positive axillary nodes (N+). The outcomes reported on different meta-analyses showed a high false negative rate (FNR) between 12-14% exceeding the security threshold of 10% ^[12,15]. For this reason, ALND is still the gold standard in those patients. Nevertheless, those meta-analyses have suggested that a minimum of 3 nodes should be recovered employing the dual technique of both blue dye and radioisotope to reduce the FNR in these patients ^[12,15].

One of the most accepted hypotheses, to explain this high FNR, is the knowledge that we have about the chemotherapy capacity for modifying and changing the lymphatic drain pathways. Because of this, the idea is to perform a previous study at the time of diagnosis and mark those affected nodes with a

clip. Through this specific evaluation, it is intended to avoid false negatives due to lymphatic pathways drainage changes. All these actions, in order to contribute to a better and more precise technique to stage the axillary disease. Thanks to this hypothesis it appeared targeted axillary dissection or TAD ^[16].

Targeted axillary dissection (TAD) has been submitted as an alternative method for axillary staging in ycN0 patients that has already demonstrated to reduce the FNR to 2-7% ^[16, 17]. TAD combines SLNB as well as the removal of the node-positive marked nodes at diagnosis (TLNB). For this new technique, it is essential to mark those nodes where there was proven metastasis disease, previously to NACT, to remove them in subsequent surgery. Experts thought that the specific evaluation of the lymph node proven to contain metastases at the time of diagnosis should improve the accuracy of nodal assessment after chemotherapy ^[18]. These affected axillary nodes are identified, biopsied, and marked by ultrasound guidance. Currently, the best marking technique has not been identified yet, although the most widely used are: clips, radioactive iodine seed, carbon tattoo, etc.

The aim of this study is to determine the technical feasibility and safety of our TAD technique and to describe the oncological results and axillary recurrence, so as this can provide more information regarding which patients may benefit from this less invasive axillary staging.

METHODS AND MATERIALS

Study design

This present study is a prospective descriptive study from 2019 to 2023 in the Breast Pathology Unity of Hospital Universitari Sant Joan De Déu, Althaia from Manresa, Spain. In our centre, TAD technique was established with the breast cancer protocol in 2017. All patients who became clinically and radiologically node-negative (ycN0) as a result of NACT and had the indication of TAD at the time of their breast surgery were included. The study was approved by the research ethics committee and informed consent was obtained before the surgical procedure.

The aim of this study is to determine the technical feasibility and safety of TAD technique by the presence or absence of technical failure (defined as absence of drainage of the double tracer and/or missing clip). Also to assess the concordance of the sentinel node with the clipped node. Finally, to describe the oncological results and axillary recurrence, so as this can provide more information regarding which patients may benefit from this less invasive axillary staging.

Eligibility and Exclusion Criteria

We selected women older than 18 years of age who met the three following criteria 1) positive diagnostic of primary invasive non metastatic breast cancer; 2) N1-N2 axillary disease confirmed by fine needle aspiration (FNA) or core needle biopsy (CNB); 3) had completed neoadjuvant treatment. Patients with distant metastases, prior axillary surgeries, pregnant, with inflammatory breast cancer or not able to have surgical treatment were excluded. Flow-chart is summarised in Fig. 1.

Extension study pre and post neoadjuvant treatment

All patients had routine imaging with mammography, ultrasound (US) and magnetic resonance imaging (MRI) at diagnosis basins per our institutional protocol. Histological proofs such as FNA or CBV were performed on the most abnormal-appearing node. In that moment, if axillary disease was identified, a clip was placed in the biopsied pathologic nodes. By the time NACT was completed, MRI and US guided FNA were performed in order to assess the response to NACT. Only patients who became clinically and radiologically node-negative were consented for TAD.

Surgical technique details

The day before surgery, a tracer dose of 99mTc was administered to patients in order to perform SLNB. Then, between 1 and 6 hours prior to surgery, US guided localization of the clipped node was performed with a hooked wire in order to identify it during the operation. Finally, immediate preoperative 3-5 ml of blue dye was injected at a periareolar level with a subsequent breast massage to dilate lymphatic drain pathways and to facilitate the tracer diffusion. The sentinel lymph nodes (SLN) were detected by the uptake of the radiolabeled colloid, the blue dye or both, removed, and submitted for pathological analyses. Any abnormal enlarged node was also considered as SLN and removed as well. In case of technical failure or any positive nodes ALND was performed immediately. The procedure is summarised in Fig. 2.

Pathological node evaluation

The removed sentinel nodes were formalin-fixed paraffin embedded tissue blocks were sectioned in sections and stained with haematoxylin and eosin for evaluation by a pathologist. The clipped node was identified, serially sectioned, and processed equally to non-clip-containing nodes. The pathology report of the clipped node was given separately. Given that this population had completed neoadjuvant therapy, any metastatic focus, including isolated tumour cells (ITCs) and micrometastases, were considered node positive.

Statistical analysis

A specific database was created to collect all the data of these patients. Data were collected prospectively from medical, surgical, radiologist and pathology reports.

For the statistical analysis, the IBM SPSS statistics 28.0 program was used. For the description of the qualitative variables, the frequencies and percentages have been objectified. For quantitative variables, the median and standard deviation if they followed the normal distribution, or the medians, minimum, maximum, and interquartile range if they did not.

RESULTS***Clinical and pathological characteristics***

The mean age of the patients was 55.21 years (range 32-82 years), and all of them were women. Regarding the cTNM clinical staging, 21 patients (91.7%) presented T1-T2 at diagnosis and all presented N1 axillary disease. In our sample, the most frequent tumour receptor of breast cancer was luminal with a total of 12 patients (50%), 9 patients (37.5%) were pure HER 2 and 3 patients (12.5) were triple negative. The clinical and pathological characteristics of the patients are summarised in Table 1.

Response to NACT

All patients received NACT regimens of anthracyclines and/or taxanes. The 13 HER2-positive patients (54.2%) also required treatment with Trastuzumab and/or Pertuzumab. 58.3% of the patients had a complete response to NACT while 37.5% had a partial response. In one patient it could not be assessed due to claustrophobia.

Surgical procedure

The main surgical approach was breast conservation therapy (BCT) performed in 19 patients (79.2%). In the remaining 5 patients (20.8%) mastectomy was performed. The characteristics of the surgical procedures performed are summarised in Table 2 and 3.

All the patients in the sample underwent TAD (clipped node + SLNB double tracer). There were no complications due to the clip marking procedure pre NACT and neither in the placement of the hooked wire on the day of the surgical intervention. The technique was effectively completed in 19 patients (79.2%). There were 10 patients (41.6%) who only required TAD due to the negativity of all the extracted lymph nodes.

The identification rate of the clip (IR-Clip) using the hooked wire was 91.6% (22 patients), with only 2 cases of missing clip (8.4%). Our sentinel nodes identification rate (IR-sen) was 87.5% (21 patients), and included uptake of blue dye, radioactive or both. We observed that in the 5 cases of technique failure (20.8%), 3 were due to not good double tracer drainage.

In relation to the 19 times where the technique TAD was effectively completed: we have observed that on 13 occasions (68.42%) the clipped node uptake blue dye and on 12 occasions (63.16%) uptake the radiotracer. Totally, on 14 patients (74.68%) the clipped node coincided as a SLN and on 5 patients (26.32%) the clipped node was not the SLN. In these 5 patients where the clipped node was not a SLN, disease was found on four occasions (80%) in any of the removed nodes of TAD. While, in the 14 patients where the clipped node was a SLN only in 5 patients (35.7%) disease was found in any of the removed nodes on TAD.

Axillary lymph node dissection

In our series, 14 patients (58.3%) required axillary ALND; 5 (35.7%) due to technical failure and 9 (64.3%) due to positivity of any of the extracted nodes. The surgical outcomes are summarised in Table 2 and 3.

Technical failure represented 35.7% of ALND indications (5 cases). The reason was: missing clip (2 cases) and absence of the double tracer drainage (3 cases). No further axillary lymph node involvement was found in any of the subsequent ALND performed. In addition, in one patient where the clip was missing, 2 of the extracted SLNs were positive due to macrometastasis, obtaining a final ypN1a staging.

Positivity of any of the nodes of TAD represented 64.3% of ALND indications (9 cases). Specifically: in 2 cases because of positivity of any SLNs; 5 due to the positivity of the clipped node and the last 2 due to the positivity of both. In the group with positivity of both, clipped and SLNs, the pathology report of ALND was ypN2a staging. In contrast, those patients where either the clipped node or the SLN were exclusively positive, no further axillary lymph node involvement was found in any of the subsequent ALND.

Apart from this, we would like to emphasise that in our series of the five patients where the ALND was performed because of the positivity of the clipped node exclusively, no further axillary involvement was found.

Pathological outcomes

The definitive anatomopathological staging was assessed in the post-chemotherapy surgical specimens. Regarding tumour size (ypT), 87.5% was between T0, Tis and T1, which shows a decrease in post-treatment tumour size with a 48.1% complete response of the primary tumour (T0).

Regarding axillary staging, 54.2% of the axillary involvement in our patients was ypN0 negative. Of the 13 cases with ypN0 staging, 3 were obtained after ALND performed due to technique failure. Therefore, the remaining 10 women, representing a total of 41.7% (95% CI 21.9-61.4), were those who benefited from a less invasive axillary approach with safe results. Within our sample, there was a case of isolated tumour cells with ypN0 (i+) staging where it was decided to also perform axillary dissection.

The final axillary staging was; in 3 patients (12.5%) ypN1mi, in 5 patients (20.8%) ypN1a due to macrometastasis and in 2 ypN2 (8.3%) due to involvement of one of the lymph nodes removed during ALND.

Follow-up and axillary recurrence

The mean follow-up was 21.13 months, with no evidence of recurrence in any patient.

DISCUSSION

The successful identification of the clipped node and the sentinel nodes as well as the reduction of FNR are indispensable elements for an efficient and safe axillary staging after NACT and avoiding unnecessary ALND.

TAD is a novel technique that is being heterogeneously performed over centres. Our technique includes the placement of a hooked wire guided by US in those axillary lymph nodes previously marked by a clip. In our sample, there were no complications in the clip and hooked wire placement. Therefore, both procedures were performed successfully, similar to what happened in other studies using hooked wire such as Kim et al. ^[19] with 20 patients and Balusubramanian et al. ^[20] with 25 patients. In contrast, in the study by Hartmann et al. ^[21] were able to place the hooked wire only on 80% of procedures.

Our identification rate of the clipped node (IR-Clip) was 91.6%. Similar outcomes were found in the studies by Kim et al. ^[19] (95.8%), Balusubramanian et al. ^[20] (92%) and Flores et al. ^[22] (88.3%). In contrast, in two other studies IR-Clip was not as high, being in Hartmann et al. ^[21] of 72% and in Kanesalingam et al. ^[23] of 78%. It is possible that this variability of results could be due to the experience of both the radiology and surgical team, as well as the material/size of clip used.

Nevertheless, it should not be forgotten that there are different studies on TAD technique with different marking methods such as radioactive seeds. This is the case of Caudle et al. ^[16], where iodine-125 seeds were injected to locate the previously clipped lymph node, 1 to 5 days prior to the surgery, with a subsequent IR-Clip of 100%. Similarly, the study by Straver et al. ^[24] (MARI) directly marked the lymph nodes that were positive at diagnosis using iodine-125 seeds, with an IR of 97%. Some important disadvantages of these procedures is that they are a source of radiation and strict regulatory protocols have been established to supervise their use.

Magnetic seeds are another localization method of the marked nodes that has been tested. This method has demonstrated high IR 100% using the Sentimag probe intraoperatively ^[25]. Furthermore, magseed has some important strengths such as less pain, more scheduling surgical flexibility and patient satisfaction ^[26]. However, its principal limitation is the elevated cost in comparison with wire and radioactive seed. ^[25-27].

All of this contributes to a more difficult implementation of these alternative localization techniques. Instead, the use of the hooked wire seems easier to implement. Its extensive experience of use in other fields, which would mean a shorter learning curve, as well as its economic feasibility are important strengths. The economic aspects need to be analysed in detail with more studies.

Our IR-sen was 87.5%, this data match with the observed in other relevant studies such as SENTINA trial (80.1%) ^[15] and ACOSOG Z1071 (92.9%) ^[12]. In addition, this last study ^[12] suggested that the use of double tracer (radiotracer and blue dye) as well as the extraction of the largest number of GS nodes significantly reduced the FNR of SLNB. Both recommendations were followed in our study with an average of 2.9 SN extracted by using the double tracer SLN.

Our clipped node concordance rate as a SLN was 73.68% (14/19 patients). In contrast, the mismatch rate was 26.32%, so in 5/19 patients the clipped node was not a SLN. Both of these results about concordance and mismatch rate are very similar to those we found in Caudle et al. ^[16] and in Flores et al ^[20]. Other studies ^[20, 23] presented a slightly better range of concordance with approximately 80% coincidence. Again, Hartmann et al. ^[21] presented very discordant results to the rest with a 35.7% mismatch rate between the clipped node and the SLN.

In the 14 patients where the clipped node coincided as a SLN, only in 35.7% (5/14) axillary disease was discovered. Instead, in the 5 patients where the clipped node hadn't double tracer drainage, 80.0% (4/5) of axillary disease was found. In these 5 patients, remaining positive nodes would have been missed if only SLNB post NACT had been performed. This increase in disease encountered when clipped node and SLN did not match may help explain the higher rate of FNR found when only SLNB post NACT is performed. This hypothesis was demonstrated in the ACOSOG Z1071 trial ^[12]. In those patients where

the clipped node coincided as a SLN, the FNR was 6.8%. But, when the clipped node was not a SLN and was removed with ALND nodes the FNR was 19.0% [12].

In our sample, in 41.6% of patients TAD was completed without technical failure or positive nodes. Therefore, these patients benefited from a less invasive axillary approach, avoiding comorbidities related with ALND. Despite the fact that in our study we were unable to calculate the FNR of TAD technique, because not all patients underwent lymphadenectomy, the results in other studies have provided safety data. Caudle et al. [16] with an FNR of 2.0% and Donker et al. [17] with an FNR of 7.0% corroborate the efficacy of the technique, making safe the omission of the ALND in these selected patients. In addition, in these patients with a mean follow-up of 21.13 months, there is no evidence of axillary recurrence.

Limitations

This study has several limitations. The main one is the small sample of patients studied. We are also limited by being a single-centre study, so more studies are needed to assess whether it could be reproduced in other institutions. In addition, our study cannot determine if TAD technique is safe in oncological terms, since our follow-up time is not long enough to corroborate non-recurrence in a proper way.

CONCLUSIONS

Our early data suggest that TAD technique with clipped nodes at diagnosis and subsequent localization using a hooked wire is a feasible and safe technique that can allow avoiding ALND in selected patients. The hooked wire implies a cost-effective technique that allows centres with less economic resources to perform TAD. Marking the positive nodes at diagnosis provides greater oncological safety and avoids false negatives that would not be detected with SNLB post NACT alone. TAD seems to have more and more evidence in favour of being a safe alternative for axillary staging N+ patients who become negative after NACT.

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Conflicts of interest: None declared.

REFERENCES

1. Arnold M, Morgan E, Rungay H, Mafra A, Singh D, Laversanne M, et al. Current and future burden of breast cancer: Global Statistics for 2020 and 2040. *The Breast*. 2022Sep2;66:15–23.

2. Beenken SW, Urist MM, Zhang Y, Desmond R, Krontiras H, Medina H, et al. Axillary lymph node status, but not tumor size, predicts locoregional recurrence and overall survival after mastectomy for breast cancer. *Ann Surg* [Internet]. 2003;237(5):732–8; discussion 738-9.
3. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010; 11(10):927–33.
4. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and Sentinel Node metastasis. *JAMA*. 2017Sep12; 318(10):918.
5. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet*. 1997; 349(9069):1864–7.
6. Noguchi M, Inokuchi M, Noguchi M, Morioka E, Ohno Y, Kurita T. Axillary surgery for breast cancer: past, present, and future. *Breast Cancer*. 2021; 28(1):9–15.
7. Che Bakri NA, Kwasnicki RM, Khan N, Ghandour O, Lee A, Grant Y, et al. Impact of axillary lymph node dissection and sentinel lymph node biopsy on upper limb morbidity in breast cancer patients: A systematic review and Meta-analysis: A systematic review and meta-analysis. *Ann Surg*. 2023;277(4):572–80.
8. Yélamos C, Montesinos F, Eguino A, Fernández B, González A, García M, et al. Impacto del linfedema en la calidad de vida de las mujeres con cáncer de mama. *Psicooncología*. 2007;4(1):143–63. Spanish.
9. Banys-Paluchowski M, Gasparri M, de Boniface J, Gentilini O, Stickeler E, Hartmann S, et al. 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*. 2021Apr;13(7):1565.
10. Hennessy BT, Hortobagyi GN, Rouzier R, Kuerer H, Sneige N, Buzdar AU, et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. *J Clin Oncol*. 2005;23(36):9304–11.
11. Dominici LS, Negron Gonzalez VM, Buzdar AU, Lucci A, Mittendorf EA, Le-Petross HT, et al. Cytologically proven axillary lymph node metastases are eradicated in patients receiving

- preoperative chemotherapy with concurrent trastuzumab for HER2-positive breast cancer. *Cancer*. 2010;116(12):2884–9.
12. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial: The ACOSOG Z1071 (alliance) clinical trial. *JAMA*. 2013;310(14):1455–61.
 13. Cao S, Liu X, Cui J, Liu X, Zhong J, Yang Z, et al. Feasibility and reliability of sentinel lymph node biopsy after neoadjuvant chemotherapy in breast cancer patients with positive axillary nodes at initial diagnosis: An up-to-date meta-analysis of 3,578 patients. *The Breast*. 2021Oct;59:256–69.
 14. Kang Y-J, Han W, Park S, You JY, Yi HW, Park S, et al. Outcome following sentinel lymph node biopsy-guided decisions in breast cancer patients with conversion from positive to negative axillary lymph nodes after neoadjuvant chemotherapy. *Breast Cancer Res Treat*. 2017;166(2):473–80.
 15. 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 Oncol*. 2013;14(7):609–18.
 16. Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: Implementation of targeted axillary dissection. *Journal of Clinical Oncology*. 2016Apr1;34(10):1072–8.
 17. 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: The MARI procedure. *Ann Surg*. 2015;261(2):378–82.
 18. Swarnkar PK, Tayeh S, Michell MJ, Mokbel 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*. 2021Mar26;13(7):1539.
 19. Kim EY, Byon WS, Lee KH, Yun J-S, Park YL, Park CH, et al. Feasibility of preoperative axillary lymph node marking with a clip in breast cancer patients before neoadjuvant chemotherapy: A preliminary study. *World J Surg*. 2018;42(2):582–9.

20. Balasubramanian R, Morgan C, Shaari E, Kovacs T, Pinder SE, Hamed H, et al. Wire guided localisation for targeted axillary node dissection is accurate in axillary staging in node positive breast cancer following neoadjuvant chemotherapy. *Eur J Surg Oncol*. 2020;46(6):1028–33.
21. Hartmann S, Reimer T, Gerber B, Stubert J, Stengel B, Stachs A. Wire localization of clip-marked axillary lymph nodes in breast cancer patients treated with primary systemic therapy. *Eur J Surg Oncol* [Internet]. 2018;
22. Flores-Funes D, Aguilar-Jiménez J, Martínez-Gálvez M, Ibáñez-Ibáñez MJ, Carrasco-González L, Gil-Izquierdo JI, et al. Feasibility and validation of the targeted axillary dissection technique in the axillary staging of breast cancer after neoadjuvant therapy: Definitive results. *Surg Oncol*. 2021;38(101636):101636.
23. Kanesalingam K, Sriram N, Heilat G, Ng E-E, Meybodi F, Elder E, et al. Targeted axillary dissection after neoadjuvant systemic therapy in patients with node-positive breast cancer. *ANZ J Surg*. 2020;90(3):332–8.
24. Straver ME, Loo CE, Alderliesten T, Rutgers EJT, Vrancken Peeters MTFD. Marking the axilla with radioactive iodine seeds (MARI procedure) may reduce the need for axillary dissection after neoadjuvant chemotherapy for breast cancer. *Br J Surg*. 2010;97(8):1226–31.
25. Harvey JR, Lim Y, Murphy J, Howe M, Morris J, Goyal A, et al. Safety and feasibility of breast lesion localization using magnetic seeds (Magseed): a multi-centre, open-label cohort study. *Breast Cancer Res Treat* [Internet]. 2018;169(3):531–6.
26. Žatecký J, Kubala O, Jelínek P, Lerch M, Ihnát P, Peteja M, et al. Magnetic marker localisation in breast cancer surgery. *Arch Med Sci* [Internet]. 2023;19(1):122–7.
27. Zacharioudakis K, Down S, Bholah Z, Lee S, Khan T, Maxwell AJ, et al. Is the future magnetic? Magseed localisation for non palpable breast cancer. A multi-centre non randomised control study. *Eur J Surg Oncol* [Internet]. 2019;45(11):2016–21.

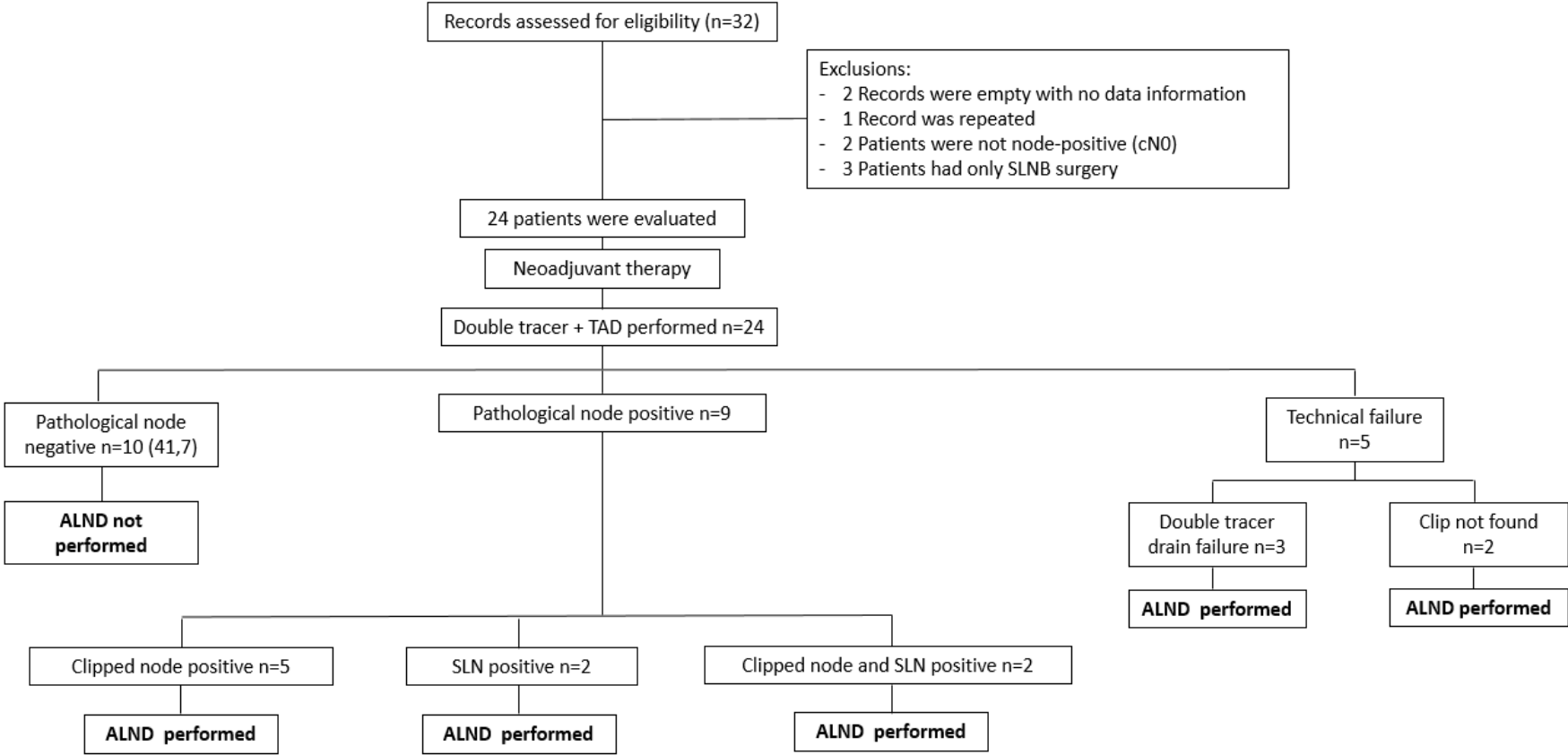


Fig. 1: Flow Chart of patients included in the study.

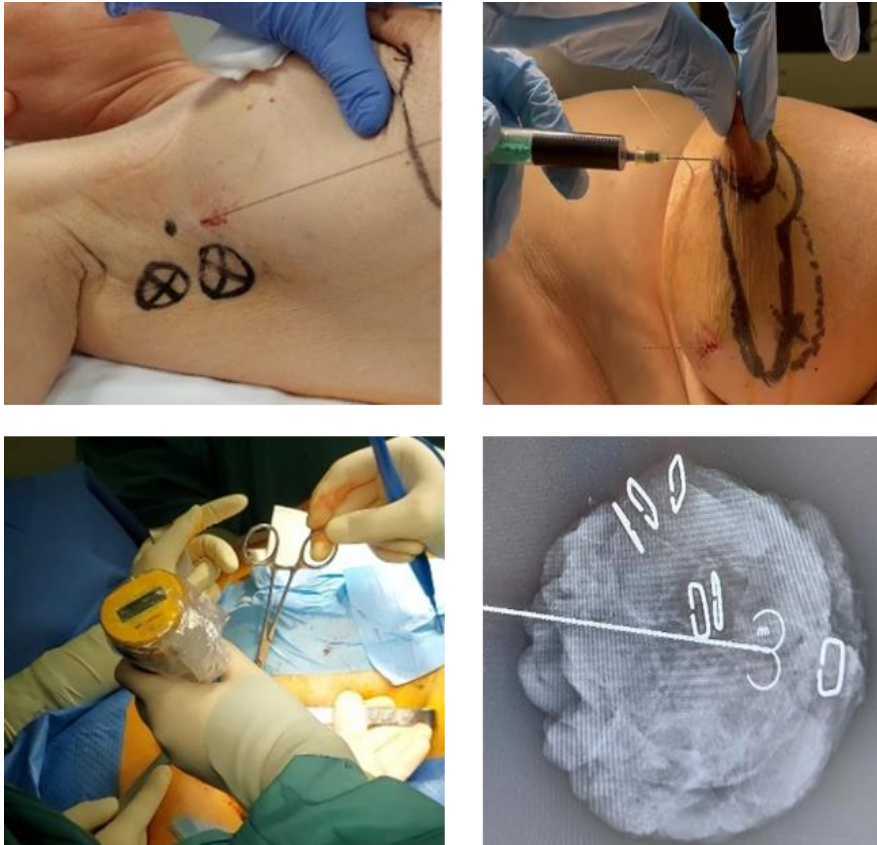


Fig. 2: Surgical procedures.

Fig 2a: Hooked wire located to identify the clipped node.

Fig 2b: Periareolar blue dye injection 5 min before surgery.

Fig 2c: Surgical excised of the corresponded nodes. Gamma probe testing one of the possible SLNs.

Fig. 2d: Specimen radiograph performed to ensure removal of the clipped node

Table 1. Clinicopathologic features

Variable	No. (%)
No. of patients	24
Age (median age, SD)	55,21 (SD 13,54)
Age range	
< 20 years	0
20-39 years	1 (4,2)
40-59 years	15 (62,5)
60-79 years	6 (25)
> 80 years	2 (8,3)
ASA scale	
ASA 1	1 (4,2)
ASA 2	21 (87,5)
ASA 3	2 (8,3)
cT	
T1	4 (16,7)
T2	17 (70,8)
T3	3 (12,5)
T4	0
cN	
N0	0
N1	24 (100)
Histology	
Invasive ductal carcinoma (IDC)	22 (91,7)
Invasive lobular carcinoma (ILC)	0
Ductal carcinoma in situ (DCIS)	2 (8,3)
Tumour receptor subtype	
Luminal Her 2 (-)	7 (29,2)
Luminal Her 2 (+)	5 (20,8)
Her 2	9 (37,5)
Triple-negative	3 (12,5)

Table 2. Surgical features and pathologic outcomes status

Variable	No. (%)
No. of patients	24
Neoadjuvant chemotherapy	
QT	10 (41,7)
QT + AntiHer2	13 (54,2)
QT + HT + AntiHer2	1 (4,2)
Response to NACT	
Complete	14 (58,3)
Partial	9 (37,5)
Type of breast surgery	
Mastectomy	5 (20,8)
Breast conservation therapy	19 (79,2)
TAD outcomes	
Negative	10 (41,7)
Positive	9 (37,5)
Technique failure	5 (20,8)
Clipped node	
Blue dye uptake	13 (68,42)
Tc ⁹⁹ uptake	12 (63,16)
Blue and/or Tc ⁹⁹ uptake	14 (74,68)
Clipped node not SLN	5 (26,32)
Axillary lymph node dissection (ALND)	
No	10 (41,7)
Yes	14 (58,3)
Indications for ALND	
Clipped node (+)	5 (35,7)
Sentinel node (+)	2 (14,3)
Clipped node + Sentinel node (++)	2 (14,3)
Technique failure + Sentinel node (+)	1 (7,1)
Technique failure	4 (28,6)
ypT	
ypT0	12 (50)
ypTis	5 (20,8)
ypT1a	2 (8,3)
ypT1c	2 (8,3)
ypT2	2 (8,3)
ypT3	1 (4,2)
ypN	
ypN0	13 (54,2)
ypN0(i+)	1 (4,2)
ypN1 mi	3 (12,5)
ypN1a	5 (20,8)
ypN2a	2 (8,3)

Table 3. Axillary surgical procedures and results and anatomopathological outcomes

Case	Clipped Node	SL nodes	Clipped node = SLN	TAD	ALND	ypTNM
1	Negative	Double tracer failure	Not assessable	Not completed	Negative	ypTisN0
2	Positive (micro)	Negative	No	Positive	Negative	ypTON1mi
3	Negative	Negative	Yes	Negative	Not indicated	ypTisN0
4	Negative	Negative	Yes	Negative	Not indicated	ypTisN0
5	Clip not found	2 SL Positive (Macro)	Not assessable	Not completed	Negative	ypT3N1a
6	Negative	Negative	Yes	Negative	Not indicated	ypT0N0
7	Negative	1 SL positive (ITC)	Yes	Positive	Negative	ypT1cN0 (i+)
8	Positive (macro)	Negative	Yes	Positive	Negative	ypTisN1a
9	Negative	Negative	No	Negative	Not indicated	ypTisN0
10	Negative	Negative	Yes	Negative	Not indicated	ypT1N0
11	Positive (micro)	Negative	Yes	Positive	Negative	ypTON1mi
12	Negative	Negative	Yes	Negative	Not indicated	ypT0N0
13	Positive (micro)	Negative	Yes	Positive	Negative	ypTON1mi
14	Negative	Negative	Yes	Negative	Not indicated	ypT0N0
15	Negative	Negative	Yes	Negative	Not indicated	ypT0N0
16	Clip not found	Negative	Not assessable	Not completed	Negative	ypT0N0
17	Negative	Double tracer failure	Not assessable	Not completed	Negative	ypT2N1a
18	Positive (macro)	Negative	Yes	Positive	Negative	ypT1cN1a
19	Negative	Double tracer failure	Not assessable	Not completed	Negative	ypT0N0
20	Negative	Negative	Yes	Negative	Not indicated	ypT0N0
21	Positive (micro)	3 SL Positive (macro-ITC-micro)	No	Positive	Positive	ypT1aN2a
22	Negative	Negative	Yes	Negative	Not indicated	ypT0N0
23	Positive (macro)	2 SL Positive (macro-micro)	No	Positive	Positive	ypT1aN2a
24	Negative	1 SL Positive (macro)	No	Positive	Negative	ypT2N1a

Acronyms

ALND	axillary lymph node dissection
BCT	breast conservation therapy
CNB	core needle biopsy
FNA	fine needle aspiration
FNR	false negative rate
IR	identification rate
IR-clip	clipped node identification rate
IR-sen	sentinel lymph node identification rate
ITC	isolated tumour cells
MRI	magnetic resonance imaging
NACT	neoadjuvant chemotherapy treatment
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
TAD	targeted axillary dissection
TLNB	targeted lymph node biopsy
US	ultrasound