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Feasibility and safety of targeted axillary dissection guided by intraoperative ultrasound after neoadjuvant treatment

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ABSTRACT

Background: Axillary management in cN + axillary nodes after neoadjuvant systemic therapy (NST) in breast cancer (BC) remains under research with the aim of de-escalation of axillary node dissection (ALND). Several axillary guided localization techniques have been reported. This study evaluates the safety of intraoperative ultrasound (IOUS) guided targeted axillary dissection (TAD) in a large sample after the results of ILINA trial.

Materials: Prospective data have been collected from October 2015 to June 2022 in patients with cT0-T4 and positive axillary lymph nodes (cN1) treated with NST. Before NST, an ultrasound visible marker was placed into the positive node. After NST, IOUS guided TAD was performed including sentinel node biopsy (SLN). Until December 2019, all patients underwent an ALND after TAD procedure. From January 2020, ALND was spared in those patients with an axillary pathological complete response (pCR).

Results: 235 patients were included. pCR (ypT0/is ypN0) was achieved in 29% patients. Identification rate (IR) of the clipped node by IOUS was 96% (95% IC, 92.5–98.1%) and IR of SLN was 95% (95% IC, 90.8–97.2%). False negative rate (FNR) for TAD procedure (SLN + clipped node) was 7.0% (95% IC, 2.3–15.7%), which decreased to 4.9% when a total of 3 or more nodes were removed. Axillary ultrasound before surgery assessed residual disease with an AUC of 0.5241. Residual axillary disease tend to be the most significant factor for axillary recurrences.

Conclusions: This study confirms the feasibility, safety and accuracy of IOUS guided surgery for axillary staging after NST in node positive BC patients.

1. Introduction

In the last decade several clinical trials have evaluated the feasibility of a less invasive surgical axillary staging strategy after neoadjuvant systemic therapy (NST) for clinically node-positive patients who converted to cN0. The routinely axillary lymph node dissection (ALND), that has been standard in positive axillary nodes before NST, causes sequelae (i.e. lymphedema, loss of nerve sensory) that decrease quality of life in breast cancer patient [1]. Nowadays, targeted therapy has increased rates of axillary pathological complete response (pCR) up to 74%, and in such cases, ALND may turn to be an unnecessary surgery [2]. Sentinel node (SLN) biopsy being a less extensive axillary surgery with lower risk of morbidity, still rise concerns as the only axillary surgery due to the very few long term results [3], as well as the awaiting results of the role of radiation therapy in this setting. Several trials (SENTINA [4], Z1071 [5], SN FNAC [6], GANEA 2 [7]) of SLNB with subsequent ALND have settled the FNR in the range of 10–14%. This FNR was considered too high in order to detect patients with residual disease after NST who could benefit from the addition of adjuvant treatments, such as radiotherapy and new systemic treatments (capecitabine [8], T-DM1 [9]) with impact on oncological outcomes.

Different strategies have been proposed to decrease the FNR below the target of 10%. Removal of 3 or more SLN, the use of dual

Abbreviations: NST, Neoadjuvant systemic treatment; pCR, Pathologic Complete Response; ALND, Axillary Lymph Node Dissection; SLNB, Sentinel Node Biopsy; TAD, Targeted axillary dissection; IOUS, Intraoperative Ultrasound.

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tracer techniques (radioactive and dyes), immunohistochemistry (IHC) lymph node evaluation and removal of the initially biopsied positive lymph node. Even though, studies have shown that removing ≥3 SLNs may not be achievable in the vast majority of patients [4,5] and in around 25% of cases the clipped node is not the SLN [10]. The latter could be solved marking the positive lymph node before initiate NST and removing it at the time of surgery besides the SLN, procedure which has been called targeted axillary dissection (TAD) [10]. Several methods for marking the positive axillary node have been described, such as wire localization, radioactive seeds, carbon dye, magnetic seeds, radar reflector or radiofrequency tag. Identification rates (IR) and FNR published varies between 92-100% and 2.0–7.0%, respectively [10–12]. Nevertheless, there are no studies comparing the different techniques, and the majority of them are chosen depending on the surgeon's discretion, or institutional resources available. Our group have already published the use of intraoperative ultrasound (IOUS) for excising the clipped axillary node with a FNR of 4% [13].

The aim of the study is to update the results of the prospective study ILINA, using IOUS for excising the clipped node in cN + breast cancer patients after NST as part of the TAD procedure as well as identifying accuracy of radiological response and results of oncological outcomes with the omission of ALND.

2. Material & Methods

From October 2015 to June 2022, patients with cytologically-proven axillary metastasis undergoing NST followed by surgery were included in this prospective study. Until December 2019, patients were included in a prospective study named ILINA study [13] approved by the Institutional Ethics Committee, which entailed TAD followed by ALND. From January 2020, patients were offered TAD and omission of ALND in case of having both negative SLNs and clipped node.

All patients had a mammogram and an US of the breast and axilla, and, in some cases, MRI. If suspicious axillary nodes were found on US, a fine-needle aspiration (FNA) was performed. Lymph nodes were considered suspicious if they showed a focal or diffuse cortical thickening (>3 mm thick) or loss of the fatty hilum. Number of suspicious nodes and morphological alteration according to BEDI criteria [14] were also recorded in each patient. In patients with cytologically-proven positive axillary nodes, a US-visible hydrogel polymer metal marker (Hydromark; Devicor Medical Products, Inc., Cincinnati, OH, USA) was placed into the biopsied node before initiating NST.

2.1. Neoadjuvant treatments

NST was administered according to institutional protocols at the discretion of the treating oncologist. Chemotherapy included anthracycline (four cycles of adriamycin + cyclophosphamide) plus a weekly (x12) taxane-based regimen. Endocrine therapy was based on aromatase inhibitors. Targeted therapy included (neo) adjuvant anti-HER2 therapy with trastuzumab ± pertuzumab when indicated or CDK 4/6 inhibitors inside a clinical trial. The time interval from placement of the clip to surgery was recorded in all patients.

Patient's response to NST was assessed by mammogram, breast and axillary US (AUS), and an MRI examination (only for patients who underwent diagnostic MRI). As mentioned above, patients with radiologic complete response by US were triaged to SLNB, IOUS-guided excision of the clipped node, and ALND inside ILINA protocol study. Since 2020, ALND was spared in some patients who had a negative clipped node and SLNs. For patients with suspicious axillary nodes after NST, an FNA was performed and, if positive, patients were triaged to ALND. In case the clip was not clearly visualized, an attempt was made to place another US hydrogel marker close to the first marker to facilitate IOUS-guided surgical excision. Although, in few cases where the clip was not visible by ultrasound, patients undergone ALND. All patients with IOUS-guided excision of the clipped node were evaluated for assessing the feasibility of the IOUS procedure, regardless of the type of axillary surgery performed.

2.2. Surgical procedure

The ILINA trial involved IOUS-guided excision of the clipped node, followed by SLNB and ALND. Most patients underwent a dual technique for SLN localization, i.e., Tc99 and blue dye (Patent Blue V, ACROS OrganicsTM or methylene blue). Blue dye was injected subareolar prior to surgery, as described elsewhere [15]. If the SLN or clipped node were not localized during surgery, a direct ALND was performed. In some cases where the SLN was not identified during surgery or the clipped node was confirmed to be positive by a preoperative FNA, the clipped node excision was attempted. Before the incision, US with a high frequency probe (7–15 MHz; MyLabTM, Esaote, Genova, Italy) was performed in multiple planes to localize the hydrogel marker. The incision was made just over the area where the clip was localized, and the distance from the skin to the clip was measured by US. IOUS-guided excision of the clip was then performed as previously described [13]. Prior to resecting the clip, the area was checked with the gamma probe to ascertain that the clipped node was the SLN. Once the clipped node was excised, we confirmed the presence of the clip by ultrasound prior to the node being sent for pathologic examination. Mammogram of the clipped node was not systematically performed if breast surgeon felt confident having excised the clip. All radioactive and blue nodes found in the axilla after removal of the clipped node were excised as SLNs.

After surgery all patients with residual axillary disease received regional node irradiation (RNI). In those patients with cN1 and a complete pathological response (ypT0/is ypN0), RNI was performed only if it was considered high risk (grade 3, initial tumor size >2 cm, <50y/o, triple negative o HER2 overexpression).

2.3. Pathological evaluation

All fresh lymph nodes were sent to the Pathology Department for intraoperative assessment. The clipped node was analyzed separately from the SLN when no concordance was found, which was specified in the pathology report. Frozen section analysis was performed on SLNs, and stained with hematoxylin and eosin. Immunohistochemical staining for cytokeratins was limited to selective use at the discretion of the pathologist. Staging of the axillary nodes was performed according to the 7th edition of the American Joint.

2.4. Statistical analysis

Statistical analysis was performed using STATA software 14.2 (StataCorp, College Station, TX, USA). AUS findings to predict axilla pathologic status was calculated with a Wilcoxon rank sum test. Response assessment by AUS was evaluated calculating AUC and NPV, defined as the number of true negatives divided by the total number of negative results. FNR of SLN and/or clipped node was defined as the number of cases where the SLN or clipped node did not show metastasis even though residual disease was present, divided by the total number of cases with persistent disease in axillary lymph nodes. Logistic regression was used to identify features associated with the inability to identify the clipped node as

SLN and to identify factors associated to disease recurrence. All tests were two-sided, with a significance level of .05. CIs for different measures were calculated using the Clopper–Pearson exact method.

3. Results

3.1. Patient characteristics

A total of 235 patients were included. Median age at the time of enrollment was 51 years (range, 28–85 years). Infiltrating ductal carcinoma was the most frequent histology in 198 (84%) patients. Almost 60% of patients were classified as stage cT2. 118 (50%) patients had palpable axillary nodes and 161 (69%) patients had 3 or less suspicious nodes on initial AUS evaluation. Neoadjuvant chemotherapy was administered in 208 (89%) patients. Breast and axilla complete clinical complete response was reported in 85 (36%) and 223 (95%) patients, respectively. Patient and tumour characteristics are specified in Table 1.

3.2. Tumour response to NST

After NST, breast conservation was performed in 151 (64%) patients. Pathological complete response (pCR) was achieved in 69 (29%) patients. Breast and axillary pathologic complete response were achieved in 78 (33%) and 92 (39%) patients, respectively. None of luminal A breast cancers achieved a pCR neither in breast nor axilla. The highest rates of pCR were in pure HER2 positive and triple negative breast cancers, reaching a breast pCR of 97% and 67% and an axilla pCR of 94% and 62%, respectively.

Median number of positive nodes was higher in ER/PR + Her2 negative tumors, as well as risk of axilla upstaging (ypN2a-3a), with a probability of 35% in luminal A and 14% in luminal B, of upstaging respectively (Table 2).

Among all patients who underwent an ALND, additional axillary positive nodes were found in patients with a previous positive TAD, regardless of type of metastasis. At least one additional positive node where found at ALND in 50% patients (3 of 6) with ITCs, 24% (5 of 21) with micrometastases and 54% (50 of 93) with macrometastases detected in either the SLN and/or clipped node.

Table 1
Patient and tumour characteristics.

	No of patients (%)
Number patients	235
Median age (years)	51 (range: 28–85)
Tumour histology	
Ductal	198 (84%)
Lobular	22 (9%)
Others	15 (6%)
Biologic subtype	
Luminal A	51 (22%)
Luminal B HER2-negative	94 (40%)
Luminal B HER2-positive	36 (15%)
HER2 positive no luminal	33 (14%)
Triple negative	21 (9%)
Clinical T stage	
Tx	2 (1%)
T1	22 (9%)
T2	142 (60%)
T3	63 (27%)
T4	6 (3%)
Clinical N stage	
N1	231 (98%)
N2	1 (0.5%)
N3	3 (1.5%)
Initial axilla physical examination	
Negative	117 (50%)
Positive	118 (50%)
Suspicious nodes on initial AUS	
<3 nodes	161 (69%)
≥3 nodes	74 (31%)
Type of neoadjuvant therapy	
Chemotherapy	131 (56%)
Chemotherapy + targeted therapy	77 (33%)
Endocrine	19 (8%)
Endocrine + targeted therapy	8 (3%)
Clinical tumour response after NST	
ycT0	85 (36%)
ycT+	150 (64%)
Clinical node response after NST	
ycN0	223 (95%)
ycN+	12 (5%)
Type of breast surgery	
BCT	151 (64%)
Mastectomy	84 (36%)

3.3. Accuracy of axillary imaging for response assessment

Initial assessment by AUS before NST, including number of initial suspicious nodes and cortical morphologic features (BEDI 4–6), was not a good predictor of pathological nodal status (*Wilcoxon test,* $p = 0.21$ and 0.59, respectively).

After NST, an axillary restaging by imaging was conducted to predict correlation with pCR. Axillary ultrasound was used to assess residual disease in the axilla showing an AUC of 0.5241.

After NST, 27 patients had suspicious nodes by AUS, before surgery an FNA was done in all that confirmed residual disease in 11 patients. After ruling out these patients, clinical complete response *(ycN0)* by imaging showed a negative predictive value (NPV) for axilla pCR of 40% (95% IC, 33.9–47.1%). Assuming that breast response could be another good surrogate of axilla response, clinical breast complete response *(ycT0)* was evaluated showing also a NPV for axilla pCR of 61% (95% IC, 50.0–72.0%).

3.4. Accuracy of TAD

A total of 141 patients were included in the ILINA trial to validate IOUS guided TAD. Besides, 94 patients with cALND for residual disease were also added to this group. After NST, patients with clinical axillary disease, loss of US visibility of the clipped node or SLN and/or clipped node not identified during surgery were excluded of analysis. A median number of 11 nodes were excised (range: 1–33) (Fig. 1).

3.4.1. SLN plus clipped node (TAD)

Median number of nodes excised was 3 (range: 1–14). FNR rate was 7.0% (5/71), which decreased to 4.9% when a total of 3 or more nodes were removed. Clipped node was not a SLN in 25% of the patients. Presence of ≥3 suspicious lymph nodes on initially ultrasound, removal of >2 SLNs, dual tracer technique for SLN localization, presence of residual nodal disease, or presence of metastases on clipped node did not predict the clipped node to be a SLN, although retrieval of 3 or more SLNs showed a trend to statistically association ($p = 0.06$) (Table 4).

3.4.2. Clipped node

Visualization and excision of the clipped node was done by IOUS (Fig. 2). The clipped node was not visualized after NST in 4 patients and, its visualization was lost during surgery in another 5 patients. Identification rate of the clipped node by IOUS was 96% (95% IC, 92.5–98.1%). In 9 patients the clipped node was negative with additional positive axillary nodes making a FNR of 12.7% for the clipped node only.

In 16 patients (7.8%) no evidence of foreign body changes were seen on pathological examination of the clipped node. In such cases, mammographic axillary views and AUS scanning were

Table 2
Response to neoadjuvant therapy according to breast cancer subtype.

	Luminal A	Luminal B HER2 neg	Luminal B HER2+	HER2+ pure	Triple negative	Global
Global pCR (ypT0/is ypN0)	0% (0/51)	7.4% (7/94)	58.3% (21/36)	93.9% (31/33)	47.6% (10/21)	29.4% (69/235)
Breast pcR (ypT0/ypTis)	0% (0/51)	9.6% (9/94)	63.9% (23/36)	97.0% (32/33)	66.7% (14/21)	33.2% (78/235)
Axillary pCR (ypN0)	0% (0/51)	25.5% (24/94)	66.7% (24/36)	93.9% (31/33)	61.9% (13/21)	39.2% (92/235)
Median residual positive nodes	3 nodes (range: 1–11)	2 nodes (range: 1–23)	1 node (range: 1–7)	1 node	1 node (range: 1–6)	2 nodes (range: 1–23)
Upstaging to ypN2-3	35.3% (18/51)	14.9% (14/94)	16.7% (6/36)	0% (0/33)	4.8% (1/21)	16.6% (39/235)

performed postoperatively, but no residual clipped nodes were identified, suggesting clip dislodgement. No association was found between pathological nodal status and absence/presence of pathological changes secondary to clip on node *(Fisher's exact test, $p = 0.37$)*.

3.4.3. SLN biopsy

To identify SLN, radiolabelled Tc99 was used in all patients and, additionally, blue dye in 90% patients (dual tracer technique). Lymphoscintigraphy was unsuccessful for SLN identification in 16 patients. SLN was not surgically identified in 12 patients. Identification rate for SLN was 95% (95% IC, 90.8–97.2%) with a median number of 3 nodes removed (range: 1–8). FNR of SLN alone was 22.5% (Table 3).

3.5. Preliminary oncological outcomes

After a median follow-up of 31 months (range: 1–75 months), 2 patients developed local recurrence, 7 (2.9%) developed locoregional + distant metastasis and 16 (6.8%) developed distant metastasis. Axillary recurrences in 6 patients, all with distant metastasis. All patients with axillary recurrences had previously an ALND for positive axillary nodes and had received RNI. Recurrences were not significantly associated to the number of suspicious axillary nodes on initial AUS (≥3 nodes) or initially locally advanced tumour stage cT3-T4, although the presence of residual axillary nodal disease showed a statistically significance trend (HR 2.38, p = 0.079).

4. Discussion

IOUS guided targeted axillary surgery has been demonstrated to be a feasible method to de-escalate axillary staging surgery in node positive breast cancer patients who undergo NST. Identification rate of the clipped node was 96% and FNR for TAD procedure was 7.0%, both figures comparable to other localization techniques for TAD (wire localization [16], radioactive seed [10], carbon tattooing [17], magnetic seed [12], radiofrequency tag [18] or radar reflector [19]) described in literature.

Our study confirms the need for surgical axillary staging that cannot be yet substituted by radiological response to NST. Current breast and axillary imaging techniques are not enough accurate to be a good predictor tool to detect nodal residual disease. A large discrepancy between AUS after neoadjuvant therapy and the pathology results of the axillary nodes was evident. One explanation could be that 35% of patients with ycN0 had limited residual disease defined as isolated tumor cell or micrometastasis, increasing the false negative results of AUS. Other problem, expressed by the radiologist, is sometimes the difficulty for differentiating between the peripheral anechoic hydrogel of the marker and the length of the cortical thickness of the lymph node that can also influence these results. In summary, AUS examination is far from considering it as a good screening method for residual disease.

Similar to previous findings [20,21], none of patients with luminal A tumors achieved a pCR, or an axillary pCR, being the group with higher risk of axillary upstaging (ypN2-3), probably reflecting the inaccurate results of axillary staging prior to systemic treatment. Better selection of patients for NST in this subgroup would be desirable. Nevertheless in neoadjuvant endocrine (NET) setting, Kantor et al. [22] have hypothesized that leaving behind a low volume of axillary disease after NET is potentially less important than after neoadjuvant chemotherapy, as NET patients have only received a small fraction of their overall endocrine therapy in the preoperative setting and no differences in OS were seen when compared this patients with upfront surgery patients with nodal disease [23]. They proposed to omit ALND in patients with fewer than three suspicious nodes before neoadjuvant endocrine therapy If only one or two nodes are positive after removal of the clipped node and two additional SLNs, the recurrence rates and survival following this Z011 like strategy are awaited.

In Her2 positive and TN negative BC, systemic treatments have contributed to an increase in pCR up to 90% in HER2 pure breast cancers in our study, similar to other published reports [24]. Tadros et al. published that nearly 90% early stage (cT1-2 cN1) HER2 and TN breast cancers, who had documented nodal metastasis before NST, were not found any residual axillary metastases when a breast pCR was confirmed. Meanwhile in the same study, patients who did not achieve a breast pCR had only a 40% probability to become node negative [25]. New strategies searching to improve preoperative identification of patients who achieved breast pCR are raising, in the aim to omit breast surgery [26]. However, any residual disease in HER2 and TN subtypes, regardless of size, is relevant to define the need of additional adjuvant treatments with survival impact [8,9]. In line with other authors [27], low volume SLN disease after NAC is not an indicator of a low risk of additional positive axillary nodes and remains an indication for cALND outside a clinical trial.

According to our results, TAD is the method that yields the lowest FNR (7%) after NST, compared to SLN biopsy or clipped node excision individually. A systematic review and pooled analysis comparing biopsy of the initial metastatic lymph node and SLN biopsy showed that both approaches were highly accurate with a FNR of 6.28% (95% CI, 3.98–9.43) and 5.18% (95% CI, 3.41–7.54), respectively [28]. This study concluded that biopsy of the clipped node alone represents a valid alternative to ALND in those node positive breast cancer patients who have responded well to upfront systemic treatment. These FNRs are significantly below the FNR for SLNB alone (13%) in the same setting [29]. Other authors advocate the optimization of SLNB procedure with dual tracer and retrieval of ≥3 SLNs, presuming the clipped node is an SLN in the majority of cases and, in the few cases the clipped node was not identified it seems not to increase the risk of developing an axillary recurrence [30]. In our study, no significant factor was found to predict concordance of SLN and clipped node, including the number of initially suspicious nodes, number of SLNs, localization technique of SLN or clipped node or axilla status after NST. This suggest again that nor SLN or clipped node must be omitted from TAD.

One concern when omitting ALND in those cN + who convert to ypN0 is the risk of regional recurrences. Retrospective studies have shown a very low risk of nodal recurrence (0–0.5%) [31,32]. In our cohort 2/6 regional recurrences occurred after a negative TAD, but

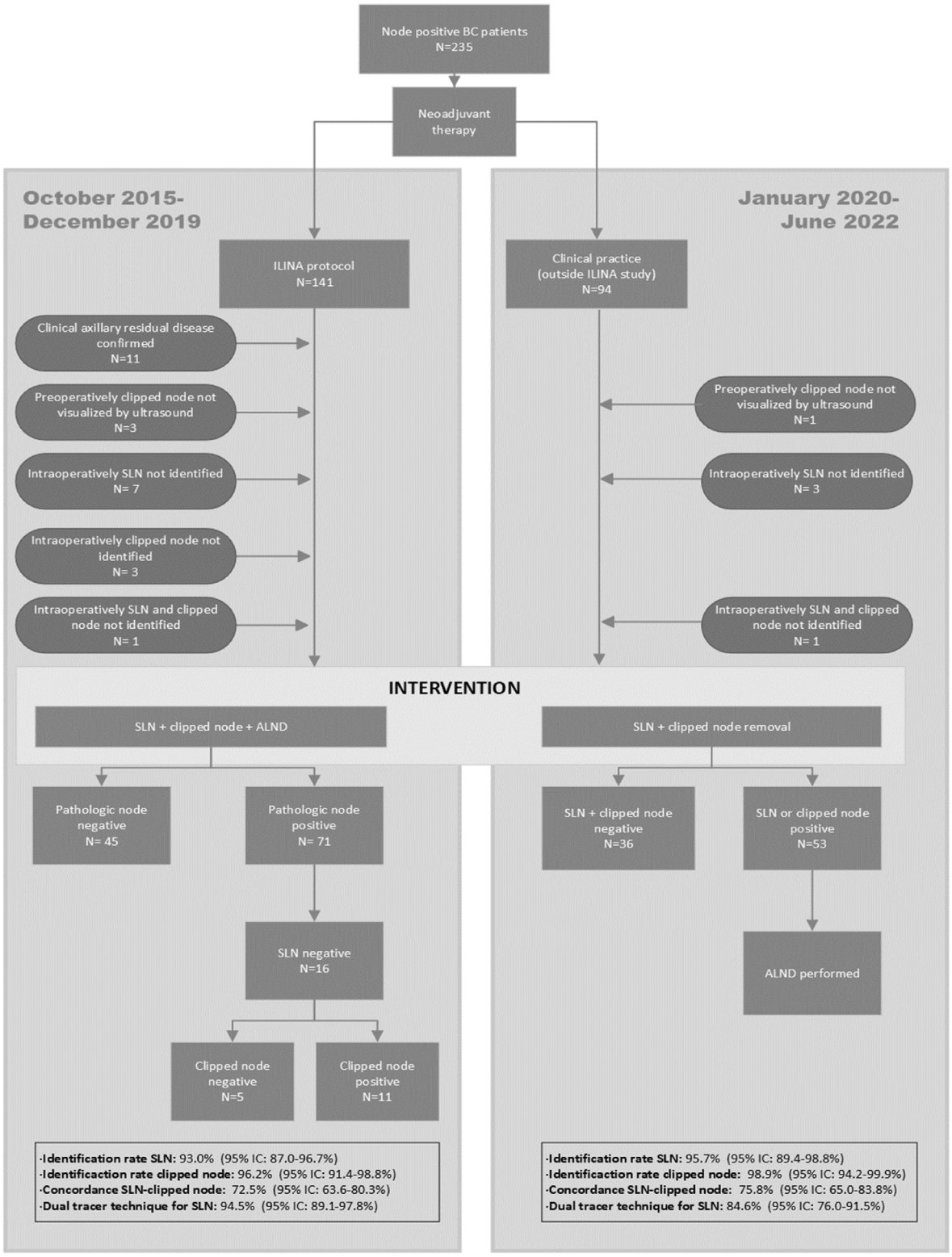

Fig. 1. Diagram of all patients included in the study. ALND axillary lymph node dissection, SLN sentinel lymph node.

in both cases with positive nodes in the ALND. This remarks how important is an accurate axillary staging in these group of patients.

Axillary residual disease seems to be the most robust risk factor for recurrence ahead of the burden of disease both in the breast and axilla. If ALND omission after an involved SLN post-NST may have an adverse effect on prognosis is still uncertain. A study analyzing National Cancer Database (NCDB) patients with residual disease in 1–3 lymph nodes (ypN1), SLNB was associated with significantly lower 5-year overall survival compared to ALND group (71% vs 77%, $p = 0.01$) [33]. Ongoing prospective randomized trials will respond

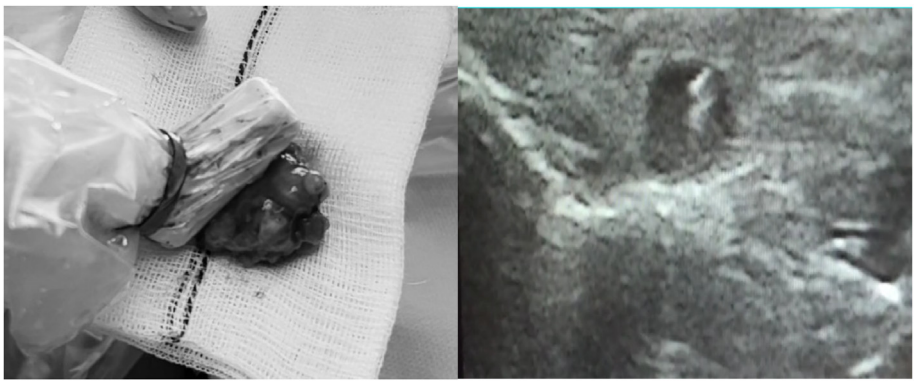

Fig. 2. Pictures of intraoperative verification of clipped node removal by ultrasound.

Table 3
False negative rates (FNR) depending on number of nodes excised.

Surgical procedure	False negative rate (%)
SLN biopsy only	FNR: 22.5% (95% IC, 13.5–33.9%) • SLNs ≤2 nodes: 26.7% (95% IC, 12.3–45.9%) • SLNs ≥3 nodes: 19.5% (95% IC, 8.8–34.9%)
Clipped node excision only	FNR: 12.7% (95% IC, 6.0–22.7%)
SLN + Clipped node excision	FNR: 7.0% (95% IC, 2.3–15.7%) • Nº nodes ≤2 nodes: 10.0% (95% IC, 2.1–26.5%) • Nº nodes ≥3 nodes: 4.9% (95% IC, 0.6–16.5%)

Table 4
Analysis of possible factors associated with concordance of clipped node and sentinel lymph node.

Variable	OR (95% CI)	P
Num. of lymph nodes suspicious initially on ultrasound		
< 3	–	0.98
≥ 3	1.01 (0.49–2.04)	
Num. of SLN removed.		
≤ 2	–	0.06
≥ 3	1.86 (0.97–3.56)	
SLN localization technique		
Tc99	–	0.58
Tc99 + blue dye (dual tracer)	0.73 (0.23–2.29)	
Presence of residual nodal disease		
Node negative	–	0.61
Node positive	0.66 (0.13–3.28)	
Metastasis in clipped node		
Absent	–	0.43
Present	1.92 (0.38–9.67)	

the need of nodal radiation after SN negative (NSBAP B51) and the role of ALND in addition to nodal radiation after SN positive (A011202) in initially node positive breast cancer patients after neoadjuvant chemotherapy.

The use of US- visible markers has made feasible the IOUS technique for excising the clip node. It can be placed directly within the cortex of axillary positive node at initial diagnosis workup, providing an exceptional visibility up to 12 months after placement in all imaging modalities (mammogram, ultrasound, MRI) [34]. It eliminates the need for a separate location procedure prior surgery creating a better patient experience.

It is the most inexpensive technique considering that other techniques demand a new and costly implantable device and a console for its localization. Reference It can be deployed after ultrasound-guided biopsy and can easily be placed inside the metastatic node, favored for its tiny size. This biopsy marker is also inert and could be left indefinitely in the body, unlike what is allowed to the radioactive seeds where is a strict time for removal according to the nuclear regulatory protocols. Contrary to magnetic seeds, it does not require non-magnetic surgical tools during surgery and does not generate an artifact in MRI sequences, which can difficult axillary or upper outer quadrant breast assessment of response.

The downside of this technique is the occasionally difficulty in visualization of the clip after NST. Clip's visibility could be compromise in case it ends within a node deep in the axilla. Loss of ultrasound visibility over time is also possible, due to reabsorption of polyethylene glycol (PEG) hydrogel coverage at the same time as lymph node cortical thickening disappears in response to systemic therapy. In that case, a new marker may be placed before surgery by the radiologist. The clip's migration is another relevant concern, consequence of an initially wrong placement by radiologist or displacement during induction therapy due to shrinkage of the metastatic node. As described previously in breast surgery, clip dislodgement during surgery is also possible [35], although uncommon, most probably because a poor tissue adherence of the hydrogel substance to fatty-lymphatic tissue, sometimes also associated to a narrow transection with electrocautery during clipped node removal.

The surgeon expertise in ultrasound guided surgery is crucial to be confident removing the clipped node without extrusion of the clipped. A surgical mammogram of the surgical specimen to confirm the presence of the clip is recommended in case of uncertainty with no clear visualization of the clip by ultrasound. It is also important to reconsider that any preoperative loco-regional anesthetic blockade in the axillary region, may interfere with the clipped node visualization. Future research may be focused on quality of life, particularly arm lymphedema rate using the TAD procedure.

5. Conclusions

In clinically node positive BC patients, IOUS guided axillary surgery after NST is feasible, safe, and an accurate method for de-escalation of axillary surgery without compromising oncologic outcomes in those patients with a pCR.

CRediT authorship contribution statement

Christian Siso: Study concepts, Study design, Funding acquisition, Quality control of data and algorithms, Formal analysis, and interpretation, Statistical, Formal analysis, Manuscript preparation, Writing – review & editing. **Antonio Esgueva:** Funding acquisition. **Joaquin Rivero:** Funding acquisition. **Clara Morales:** Funding acquisition. **Ignacio Miranda:** Funding acquisition. **Vicente Peg:** Funding acquisition. **Antonio Gil-Moreno:** Funding acquisition. **Martin Espinosa-Bravo:** Funding acquisition. **Isabel T. Rubio:** Study concepts, Funding acquisition, Formal analysis, and interpretation, Writing – review & editing, Manuscript review.

Declaration of competing interest

All authors declare that they have no potential conflicts of interest to declare.

References

[1] DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013;14(6):500–15.

[2] Dominici LS, Negron Gonzalez VM, Buzdar AU, 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.

[3] Kahler-Ribeiro-Fontana S, Pagan E, Magnoni F, et al. Long-term standard sentinel node biopsy after neoadjuvant treatment in breast cancer: a single institution ten-year follow-up. Eur J Surg Oncol 2021;47(4):804–12.

[4] Kuehn T, Bauerfeind I, Fehm T, 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.

[5] Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013;310(14):1455–61.

[6] Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol 2015;33(3):258–64.

[7] Classe JM, Loaec C, Gimbergues P, 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 Res Treat 2019;173(2):343–52.

[8] Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017;376(22):2147–59.

[9] von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019;380(7):617–28.

[10] Caudle AS, Yang WT, Krishnamurthy S, 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. J Clin Oncol 2016;34(10):1072–8.

[11] Donker M, Straver ME, Wesseling J, et al. Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. Ann Surg 2015;261(2):378–82.

[12] Mariscal Martinez A, Vives Rosello I, Salazar Gomez A, et al. Advantages of preoperative localization and surgical resection of metastatic axillary lymph nodes using magnetic seeds after neoadjuvant chemotherapy in breast cancer. Surg Oncol 2021;36:28–33.

[13] Siso C, de Torres J, Esgueva-Colmenarejo A, et al. Intraoperative ultrasound-guided excision of axillary clip in patients with node-positive breast cancer treated with neoadjuvant therapy (ILINA trial) : a new tool to guide the excision of the clipped node after neoadjuvant treatment. Ann Surg Oncol 2018;25(3):784–91.

[14] Bedi DG, Krishnamurthy R, Krishnamurthy S, et al. Cortical morphologic features of axillary lymph nodes as a predictor of metastasis in breast cancer: in vitro sonographic study. AJR Am J Roentgenol 2008;191(3):646–52.

[15] Wilson LL, Giuliano AE. Sentinel lymph node mapping for primary breast cancer. Curr Oncol Rep 2005;7(1):12–7.

[16] 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 2018;44(9):1307–11.

[17] Patel R, MacKerricher W, Tsai J, et al. Pretreatment tattoo marking of suspicious axillary lymph nodes: reliability and correlation with sentinel lymph node. Ann Surg Oncol 2019;26(8):2452–8.

[18] Malter W, Eichler C, Hanstein B, Mallmann P, Holtschmidt J. First reported use of radiofrequency identification (RFID) technique for targeted excision of suspicious axillary lymph nodes in early stage breast cancer - evaluation of feasibility and review of current recommendations. In Vivo 2020;34(3):1207–13.

[19] Gallagher KK, Iles K, Kuzmiak C, Louie R, McGuire KP, Ollila DW. Prospective evaluation of radar-localized reflector-directed targeted axillary dissection in node-positive breast cancer patients after neoadjuvant systemic therapy. J Am Coll Surg 2022;234(4):538–45.

[20] Esgueva A, Siso C, Espinosa-Bravo M, et al. Leveraging the increased rates of pathologic complete response after neoadjuvant treatment in breast cancer to de-escalate surgical treatments. J Surg Oncol 2021;123(1):71–9.

[21] Fernandez-Gonzalez S, Falo C, Pla MJ, et al. Predictive factors for omitting lymphadenectomy in patients with node-positive breast cancer treated with neo-adjuvant systemic therapy. Breast J 2020;26(5):888–96.

[22] Kantor O, Wakeman M, Weiss A, et al. Axillary management after neoadjuvant endocrine therapy for hormone receptor-positive breast cancer. Ann Surg Oncol 2021;28(3):1358–67.

[23] Kantor O, Wong S, Weiss A, Metzger O, Mittendorf EA, King TA. Prognostic significance of residual nodal disease after neoadjuvant endocrine therapy for hormone receptor-positive breast cancer. NPJ Breast Cancer 2020;6:35.

[24] Nitz UA, Gluz O, Christgen M, et al. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR- phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab +/- weekly paclitaxel. Ann Oncol 2017;28(11):2768–72.

[25] Tadros AB, Yang WT, Krishnamurthy S, et al. Identification of patients with documented pathologic complete response in the breast after neoadjuvant chemotherapy for omission of axillary surgery. JAMA Surg 2017;152(7):665–70.

[26] Tasoulis MK, Lee HB, Yang W, et al. Accuracy of post-neoadjuvant chemotherapy image-guided breast biopsy to predict residual cancer. JAMA Surg 2020;155(12):e204103.

[27] Moo TA, Edelweiss M, Hajiyeva S, et al. Is low-volume disease in the sentinel node after neoadjuvant chemotherapy an indication for axillary dissection? Ann Surg Oncol 2018;25(6):1488–94.

[28] 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 (Basel) 2021;13(7).

[29] El Hage Chehade H, Headon H, El Tokhy O, Heeney J, Kasem A, Mokbel K. Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients. Am J Surg 2016;212(5):969–81.

[30] Montagna G, Lee MK, Sevilimedu V, Barrio AV, Morrow M. Is nodal clipping beneficial for node-positive breast cancer patients receiving neoadjuvant chemotherapy? Ann Surg Oncol 2022;29(10):6133–9.

[31] Wong SM, Basik M, Florianova L, et al. Oncologic safety of sentinel lymph node biopsy alone after neoadjuvant chemotherapy for breast cancer. Ann Surg Oncol 2021;28(5):2621–9.

[32] Barrio AV, Montagna G, Mamtani A, et al. Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy-A rare event. JAMA Oncol 2021;7(12):1851–5.

[33] Almahariq MF, Levitin R, Quinn TJ, et al. Omission of axillary lymph node dissection is associated with inferior survival in breast cancer patients with residual N1 nodal disease following neoadjuvant chemotherapy. Ann Surg Oncol 2021;28(2):930–40.

[34] Sun J, Henry DA, Carr MJ, et al. Feasibility of axillary lymph node localization and excision using radar reflector localization. Clin Breast Cancer 2021;21(3):e189–93.

[35] Klein RL, Mook JA, Euhus DM, et al. Evaluation of a hydrogel based breast biopsy marker (HydroMARK(R)) as an alternative to wire and radioactive seed localization for non-palpable breast lesions. J Surg Oncol 2012;105(6):591–4.