Surgical Oncology 30 (2019) 52–57

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Validation of the targeted axillary dissection technique in the axillary staging of breast cancer after neoadjuvant therapy: Preliminary results

Diego Flores-Funes[a,f,*], José Aguilar-Jiménez[a,f], María Martínez-Gálvez[b,f], María José Ibáñez-Ibáñez[c,f], Luis Carrasco-González[a,f], José Ignacio Gil-Izquierdo[b,f], María Asunción Chaves-Benito[d,f], Francisco Ayala-De La Peña[e,f], Andrés Nieto-Olivares[d,f], José Luis Aguayo-Albasini[a,f]

[a] General Surgery Department, Morales Meseguer University Hospital, Murcia, Spain
[b] Radiology Department, Morales Meseguer University Hospital, Murcia, Spain
[c] Nuclear Medicine, Morales Meseguer University Hospital, Murcia, Spain
[d] Pathology Department, Morales Meseguer University Hospital, Murcia, Spain
[e] Hematology and Oncology Department, Morales Meseguer University Hospital, Murcia, Spain
[f] University of Murcia, Faculty of Medicine, IMIB-Arrixaca, "Mare Nostrum" International Excellence Campus, Murcia, Spain

ARTICLE INFO

Keywords:
Breast cancer
Targeted axillary dissection
Neoadjuvant chemotherapy

ABSTRACT

Aim.: To study the feasibility and validity of ultrasound-guided pre-chemotherapy marking of metastatic axillary lymph nodes followed by targeted axillary dissection (TAD), in breast cancer patients undergoing neoadjuvant chemotherapy (NACT).

Material and method: Prospective diagnostic test study conducted between January 2016 and March 2018. Patients with breast cancer and indication for NACT, cN1 or cN2 axillary staging, were included. A clip was placed in the affected lymph node prior to NACT. A sentinel lymph-node biopsy (SLNB) and a clipped lymph-node biopsy (BCLIP) were conducted, followed by axillary lymph node dissection (ALND). Location rate (LR) and negative predictive value (NPV) were evaluated, taking SLNB, BCLIP and their combination (TAD) as evaluated tests and metastatic involvement in the ALND specimen as the gold standard.

Results: Twenty-three patients were included in the study. Sentinel lymph node could only be detected in 19 cases (LR = 80.61%), whereas BCLIP was successful in 22 (LR = 95.65%). The sentinel lymph node coincided with the marked lymph node in 14 patients (60.9%). We found a NPV for the SLNB of 0.85 (95%CI: 0.61–1.0), whereas for TAD it was 1.00 (95%CI: 0.74–1.0).

Conclusion: TAD is a feasible test for axillary restaging after NACT, with a higher success rate than SLNB.

1. Introduction

Axillary lymphadenectomy (ALND) as a locoregional treatment in breast cancer is associated with considerable morbidity, such as the appearance of lymphoedema, paresthesias and motor alterations of the upper limb [1,2]. In patients with locally advanced breast cancer the main treatment is neoadjuvant chemotherapy (NACT) with subsequent surgical treatment of the tumor together with ALND. However, axillary complete response (pCR) rates of 40–50% after NACT in some series [3–5] have prompted the possibility of sparing ALND in this group of patients (or in an adequately selected subgroup).

For this reason various work groups began looking for a feasible and reproducible method to stage the axilla in patients receiving NACT. The most evident approach is selective sentinel lymph-node biopsy (SLNB) after NACT. However, although some series had promising results, with a false-negative rate (FNR) of around 7–11% [6,7], most studies yielded a rate closer to 15–20% [4,8–10], which was considered unacceptable. The ACOSOG Z1071 multicentre trial [3], conducted in more than 700 patients, identified an FNR of 12.6%, which somehow invalidated SLNB as a reliable staging method in N+ patients undergoing NACT. However, a subgroup analysis in other studies yielded more favourable FNRs in patients with negative hormone receptors and positive HER2 [9], and in the triple-negative group [4], which prompted the possibility of a more adequate post-NACT SLNB according to the molecular profile of the tumor.

After the deficient results obtained with the use of SLNB in these

* Corresponding author. Dirección: Avda. Marqués de los Vélez, S/N, 30008, Murcia, Spain.
E-mail address: diego.flores@um.es (D. Flores-Funes).

https://doi.org/10.1016/j.suronc.2019.05.019
Received 28 July 2018; Received in revised form 19 November 2018; Accepted 25 May 2019
0960-7404/

patients, other methods were studied with a view to reducing the FNR. Pre-NACT location of the affected lymph node with a marker (a clip or radiotracer) and then, during surgery, performing both SLNB and resection of the marked lymph node (BCLIP) has come to be known as targeted axillary dissection (TAD). The ACOSOG Z1071 trial [11] defined a subgroup of patients in whom the lymph node seen to be metastatic was marked with a clip and found an FNR of 6.8% in the cases where the clipped node was identified as one of the sentinel lymph nodes, compared to an FNR of 14.3% if the clip was not found and 19.0% if the clipped node was within an ALND specimen. Other recent studies, notably the one by Caudle [12], found an even lower FNR (2%) in patients guaranteed excision of the previously affected and marked lymph node together with conventional SNLB (using a double tracer). These results suggest that resection of the initially affected and radiologically marked lymph node might, together with the usual SLNB, be a reliable method of axillary staging.

A study was published recently on the feasibility of clip marking in 20 patients [13]. The study concludes that it is a feasible and reproducible technique and improves axillary restaging after NACT. However, the difficulty of the technique and the small number of publications calls for further studies to validate the technique and confirm feasibility, similar to the validation studies that led to the widespread practice of SLNB in early breast cancer.

The aim of the present study is to conduct a preliminary analysis of the feasibility and validity of axillary restaging in breast cancer patients undergoing NACT with initially positive axilla. For this we use metastatic lymph node marking with an ultrasound-guided clip and, during surgery, TAD. Our fundamental aim is to discover the location rate (LR) and false-negative rate (FNR) with this technique.

2. Material and methods

This descriptive single-centre study, with data collected prospectively, was conducted between January 2016 and March 2018. The study was approved by the ethics committee and written informed consent was obtained from the patients. All the consecutive cases of breast cancer with an indication for NACT and cN1 or cN2 axillary staging confirmed by US-guided fine needle aspiration (FNA) were included. All those with previous axillary surgery, cN0 stage, cN2 with adenopathic conglomerate on palpation and cN3 were excluded.

All the patients included in the study had a clip placed at the time of diagnosis and staging, prior to NACT, in both the tumor and the suspected axillary lymph node with positive FNA. In one case we used a metallic clip with hydrogel (HydroMark®) and in the rest a braided nitinol clip (Tumark®) similar to the one used for tumor marking. US-guided placement of these markers was directed to the cortex of the affected node(s) in the area of maximum thickness. Placement and subsequent ultrasonographic confirmation was performed by 2 radiologists experienced in breast pathology. After completion of NACT the clinical response of the tumor and axilla was observed according to RECIST 1.1 criteria [14] using new imaging techniques (mammography, ultrasonography and NMR of the breast), which were compared to previous imaging tests. To perform SLNB we administered a periareolar intra/subdermal injection of a tracer dose of 99mTc-labelled albumin nanocolloids (Nanocoll®) prior to surgery (less than 24 h), after which anteroposterior and lateral images of the chest were obtained with lymphatic gammagraphy between 60 and 120 min after injection (eCAM®, Siemens). Intraoperative identification of the sentinel lymph node was done with a gamma detection probe (Neoprobe 2000®). All the sentinel lymph nodes were removed until the number of radiation counts in the axilla was less than 10% of the counts of the node with greatest activity. For BCLIP, we locate the clipped node using preoperative US-guided wire location (Figs. 1 and 2).

During the surgical operation, performed by any one of the 5 surgeons in our Hospital's Breast Unit, we carried out the BCLIP and SLNB (which in some cases coincided with the marker-clipped node). Any of the biopsied nodes with a metastatic focus, including micrometastases, determined intraoperatively using One-Step Nucleic Acid Amplification (OSNA), was considered “positive”. Following this, the corresponding breast surgery and ALND were performed in all the patients independent of the TAD result.

The surgical specimens were sent independently to our hospital's Pathological Anatomy service, where 2 experienced breast pathologists conducted an intraoperative assessment of the sentinel lymph node and marker-clipped lymph node retrieved with the OSNA method. The ALND specimen was also processed and cut to detect the total number of lymph nodes included and how many of them were metastatic. We also calculated the pathological response using the SYMMANS method [15] and the final staging of the tumor according to the TNM system of the American Joint Committee on Cancer (AJCC), 7th edition [16].

Ultrasonographic variables of lymph-node morphology were collected, together with clinical and tumor variables. Ultrasound was used to specify the size and cortex thickness of the suspected axillary lymph node. The tumor pathology features were: laterality and quadrant of the tumor; size of the tumor in centimetres (cm), measured by magnetic resonance; cTN classification and tumor stage; histological type (ductal, lobular, undetermined); histological grade (Bloom-Richardson [17]); hormone receptor positivity and HER2; and regime and duration of the chemotherapy treatment. To assess the degree of response to chemotherapy we considered: tumor size in cm after completion of treatment; ycTN classification; clinical response to chemotherapy (evaluated by mammography, ultrasonography and MR) according to RECIST 1.1 criteria [14]; type of surgery (conservative, simple mastectomy or modified radical mastectomy); whether or not lymphadenectomy was performed; ypTN classification and pathological response using the SYMMANS method [15]. The parameters for assessing the feasibility

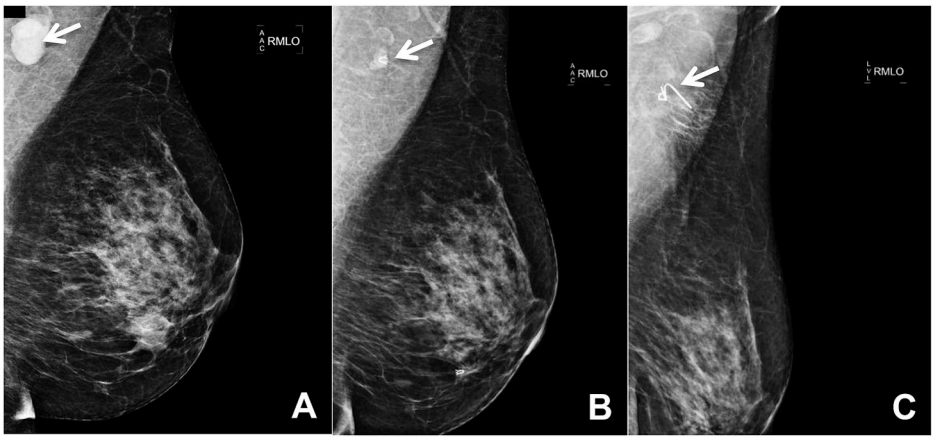

Fig. 1. Mammograms of a patient included in the study. (A) Mammography at diagnosis, with an enlarged lymph node (arrow). (B) Mammography after clip colocation and NACT, with a considerable decrease of the lymph node (arrow). (C) Mammography after preoperative US-guided wire location. The wire is observed in clipped lymph node (arrow).

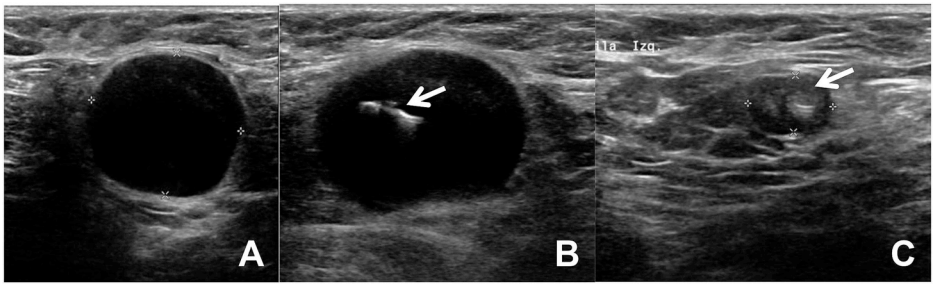

Fig. 2. Axillary ultrasound images of another patient included in the study. (A) Enlarged lymph node at diagnosis, with a major diameter of 2.8 cm. (B) Lymph node after colocation of clip (arrow). (C) The same lymph node after NACT, with a partial response and a major diameter of 1.2 cm (arrow).

and validation of TAD were: technical limitations in placing the pre-surgical hooked wire and associated complications; complications during the procedure; number of sentinel lymph nodes extracted; number of positive sentinel lymph nodes; intraoperative location of the clipped lymph node; coincidence of the marker-clipped node with the sentinel lymph node(s); result of the pathological analysis of each biopsied node; number of metastatic nodes; and total number of nodes retrieved in the ALND.

With the latter variables a preliminary analysis was done of sensitivity, specificity, positive and negative predictive value (PPV and NPV respectively), false-positive (FPR) and false-negative rates (FNR), and positive (PLR) and negative likelihood ratios (NLR). The tests used were SLNB, BCLIP and TAD (combination of the first two, taking the negativity of both as negative and the positivity of at least one of them as positive); the Gold Standard was metastatic involvement in the ALND after TAD (considering positive ALND if, after TAD was performed, at least 1 metastatic lymph node was found in pathological analysis). We also performed a Bayesian equivalence analysis, expressing the results as pre-test and post-test probabilities. Calculation of the sample size shows that a sample of 59 patients is necessary for a 40% prevalence of affected nodes in the lymphadenectomy, assuming an absolute error associated with an estimate of 10%, which means the definitive results will be published when the sample size is reached.

Data are expressed as absolute and relative frequencies for the qualitative variables and as mean and 95% confidence interval (CI95%) for the continuous quantitative variables and median and interquartile range (IQR) for the discrete quantitative variables. The IBM software package SPSS© version 22 was used for data collection and descriptive analysis of the variables. To analyse sensitivity, specificity, predictive values and probability coefficients we used the software Epidat 3.1.© from the Conselleria de Sanidade de la Xunta de Galicia, Spain [18]. The STARD 2015 guidelines [19] were followed in the writing of this article.

3. Results

Lymph-node clip marking was done in 50 patients during the time period mentioned. 11 were cN0 (ultrasound suspicion with negative FNA), for which reason ALND was not performed and they were not included in the study; 6 received direct ALND without SLNB or TAD as no clinical lymph-node response was recorded, not even on imaging; and 2 patients were excluded for being cN3 and cM1. The remaining 23 cases were included in the study (Fig. 3).

The demographic data, tumor characteristics, molecular profile and staging are shown in Table 1. The NACT used and tumor response according to RECIST criteria can be seen in Table 2.

The technique for marking the metastatic lymph node with a clip was performed in all cases without technical difficulties or complications, whereas the technique for preoperative US-guided wire location did present difficulties in correctly locating the clipped node in 2 cases (8.7%), due to clipped node could not be easily identified. There were no complications in the procedure. As far as surgery is concerned, tumor resection was conservative in 16 patients (69.6%), whereas 7 cases (30.4%) required a modified radical mastectomy after TAD due to

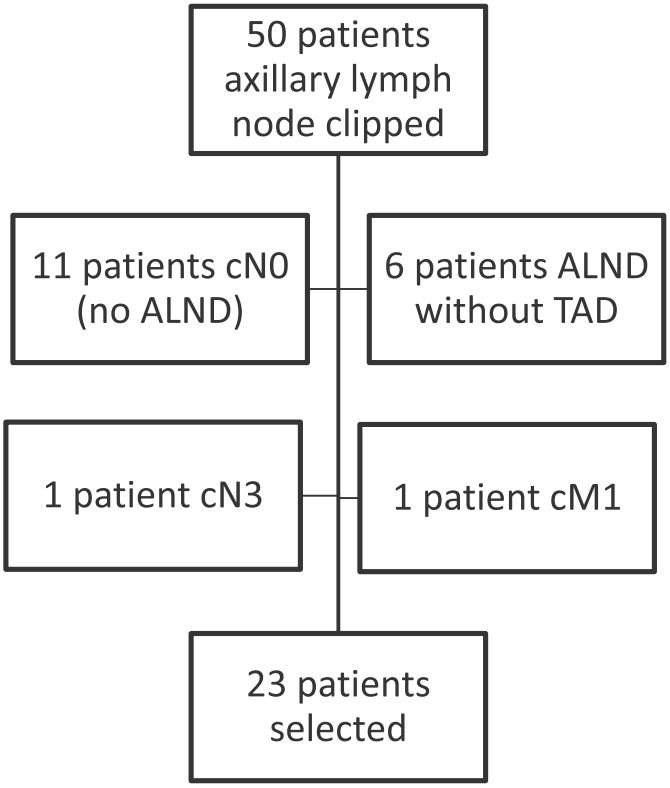

Fig. 3. Flowchart with patients included and excluded in the study. ALDN: Axillary Lymph Node Dissection. TAD: Targered Axillary Dissection.

multicentricity, tumor size or express wishes of the patient. The most common surgical complication was local seroma (4 patients, 17.4%). One patient (4.3%) required reoperation for a haematoma in the surgical bed of the breast, which led to anaemia and hypotension (Table 3).

As for the SLNB, BCLIP, TAD and subsequent ALND findings, the results were as follows: in the SNLB at least 1 sentinel lymph node was located in 19 patients (LR: 80.6%), whereas the remaining 4 revealed no sentinel lymph nodes on gammagraphy or in the surgical exploration with a gamma probe, for which reason the technique was considered a failure; the BCLIP was successful in 22 cases (LR: 95.7%), with one failure to locate the clipped node (it was subsequently found in the surgical specimen from the modified radical mastectomy); the sentinel lymph node coincided with the marked lymph node in 14 patients (60.9%); the sentinel lymph node was negative in 13 patients (68.4%),

Table 1
Characteristics of patients and pathological variables of the tumor at diagnosis.

Variable		Frecuency/Mean/ Median
Age (years)		55 (95%CI 50-59)
Tumor side	Right	10 (43.5%)
	Left	13 (56.5%)
Quadrant location	Superior + external	10 (43.5%)
	Superior + internal	6 (26.1%)
	Inferior + external	3 (13.0%)
	Inferior + internal	4 (17.4%)
Tumor size (cm)		2.9 (95%CI 2.1–3.7)
Size of clipped node cortex (mm)		6.0 (95%CI 4.9–8.6)
cT	1	10 (43.5%)
	2	9 (39.1%)
	3	4 (17.4%)
cN	1	11 (47.8%)
	2	12 (52.2%)
Stage	IIA	3 (13.0%)
	IIB	8 (34.8%)
	IIIA	10 (43.5%)
	IIIB	1 (4.3%)
	IIIC	1 (4.3%)
Histology	Infiltrating ductal	19 (82.6%)
	Infiltrating lobular	2 (8.7%)
	Indeterminate	2 (8.7%)
Bloom-Richardson Histological Grade	1	2 (8.7%)
	2	8 (34.8%)
	3	13 (56.5%)
Hormonal receptors	Positive	17 (73.9%)
	Negative	6 (26.1%)
HER2	Positive	12 (52.2%)
	Negative	11 (47.8%)
Molecular Profile	Luminal A	7 (30.4%)
	Luminal B	9 (39.1%)
	HER2+	3 (13.0%)
	Basal-Like	4 (17.4%)

whereas the clipped node was negative in 12 (52.2%); in 15 patients (65.2%) the ALND specimen had no affected lymph node; finally, 12 patients (52.2%) met the criteria for complete response to NACT in the pathological examination (Table 4).

The results of the diagnostic test study taking the pathological stage of the ALND as the Gold Standard are summarised in Table 5. In the SLNB we found a sensitivity of 0.60 (CI95% 0.07–1.0) and an NPV of 0.92 (CI95% 0.72–1.0), which is also reflected in the likelihood ratios. The pre-test probability (prevalence of positive ALND) in the SLNB was 0.26 (CI95% 0.09–1.0), whereas in the BCLIP it was 0.32 (0.14–0.55). The combination of the two tests (TAD) did not modify the values obtained on BCLIP performed in isolation.

Table 3
Technical difficulties, complications, and characteristics of the surgical technique of the included patients.

Clip placement difficulty		0 (0.0%)
Clip placement complications		0 (0.0%)
Pre-operative wire colocation difficulty		2 (8.7%)
Wire colocation complications		0 (0.0%)
Surgery	Conservative	16 (69.6%)
	Modified radical mastectomy	7 (30.4%)
Surgical complications	No	16 (69.6%)
	Seroma	4 (17.4%)
	Haematoma	1 (4.3%)
	Surgical site infection	1 (4.3%)
	Affected margins	1 (4.3%)

4. Discussion

We present the preliminary results of a diagnostic test study designed to validate TAD in our hospital environment, with a view to revealing the trend of TAD results (high location rate and high negative predictive value) as reported in previous studies. We expect to publish the final results within 1–2 years.

It is first of all worth noting the high frequency of complete tumor response to NACT according to RECIST criteria (34.8%) and a high pCR (52.2%), in contrast to that reported by Chang (pCR 17%) in N-positive patients [20]. Moreover, 18 patients (78.3%) had a complete clinical and ultrasonographic axillary response, with no pathological nodes observed in the post-NACT follow-up. Some factors appear to contribute to these good results, such as younger age, HER2 positivity and ductal histology of the tumor [21]. This demonstrates the importance of proper restaging after neoadjuvant treatment, because the response rate is very high and these patients could benefit from being spared surgery on the axilla [22]. However, to be sure, it would be necessary to study the recurrence, overall survival and specific tumor rates at 5 years.

Secondly, our results show the feasibility and reproducibility of pretreatment clip marking, with no technical difficulties or complications during the procedure, as reported in the feasibility study by Kim [13]. Presurgical US-guided wire location of the clipped node presented technical difficulties in 2 cases. Location with a hooked wire may certainly present technical difficulties but having an experienced radiologist perform the procedure, a high rate of intraoperative detection and a lower cost makes presurgical wire location the usual procedure in our environment, as it is for Kim [13] and Plecha [23]. One possibility of improving the location of the clipped node is the use of intraoperative ultrasonography, as described by Siso [24], who presents a series of 46 patients with just 2 failures to identify the clipped node.

Table 2
Regimen, duration and response of the NACT. NACT: Neoadjuvant Chemotherapy.

Variable		Frecuency/Mean
NACT duration (months)		5.5 (95%CI 4.6–6.4)
Chemotherapy regimen	Adriamycin, Cyclophosphamide, docetaxel.	9 (41.0%)
	Pertuzumab, Trastuzumab, Docetaxel, Carboplatin.	11 (50.0%)
	Paclitaxel, Carboplatin, Adriamycin, Cyclophosphamide	2 (9.0%)
Tumor size post-NACT		0.8 (95%CI 0–1.7)
Size of clipped node cortex post-NACT (mm)		3.4 (95%CI 1.2–5.6)
ycT	0	9 (39.1%)
	1	11 (47.8%)
	2	2 (8.7%)
	3	1 (4.3%)
ycN	0	18 (78.3%)
	1	5 (21.7%)
RECIST	Complete response	8 (34.8%)
	Partial response	13 (56.5%)
	Stable disease	2 (8.7%)
	Disease progression	0 (0%)

Table 4
Evaluation parameters of the SLNB, BCLIP, TAD, ALND, and final staging with pathological response criteria. Note there are more lymph nodes in BCLIP that in SLNB, due to a failure of SLNB in 4 cases. SNLB: Sentinel Lymph Node Biopsy. BCLIP: Clipped Lymph Node Biopsy. TAD: Targered Axillary Dissection. ALND: Axillary Lymph Node Dissection.

Number of sentinel lymph nodes	0	4 (17.4%)
	1	8 (34.8%)
	2	5 (21.7%)
	3	3 (13.0%)
	4	3 (13.0%)
Clip location	Sentinel lymph node	14 (60.9%)
	No sentinel lymph node	9 (39.1%)
	ALND specimen	0 (0.0%)
SLNB result	Positive	6 (31.6%)
	Negative	13 (68.4%)
BCLIP result	Positive	11 (47.8%)
	Negative	12 (52.2%)
TAD result (SNLB + BCLIP)	Positive	11 (47.8%)
	Negative	12 (52.2%)
ALND result	Positive	8 (34.8%)
	Negative	15 (65.2%)
Number of lymph nodes in ALND specimen	(median + IQR)	11 (IQR 12)
Number of positive lymph nodes in ALND specimen	(median + IQR)	0 (IQR 9)
ypT	0	9 (39.1%)
	1	8 (34.8%)
	2	4 (17.4%)
	3	2 (8.7%)
ypN	0	12 (52.2%)
	1	6 (26.1%)
	2	5 (21.7%)
RCB (Symmans)	0 (pCR)	12 (52.2%)
	I	6 (26.1%)
	II	4 (17.4%)
	III	1 (4.3%)

Other methods for locating the affected lymph node, such as the use of paramagnetic clips, ultrasound with microbubble contrast or marking with radioactive seeds, are still being researched [25].

Thirdly, we found that the success rate of BCLIP is higher than with SLNB, as it managed to correctly stage 3 cases in which SLNB had not been effective. BCLIP only failed in 1 case, when the clipped node was inadvertently incorporated into the mastectomy specimen, probably due to wire displacement outside the node. Siso [24] and Kim [13] reported just one failure to operatively locate the clipped node, which is in line with our results. Moreover, in almost 40% of the cases the clipped node does not coincide with the sentinel lymph node, a percentage similar to that of other studies [12,24].

Fourthly, BCLIP presents significantly better predictive values than SLNB. Both specificity and the PPV are low enough to be able to suitably appreciate a positive result. However, no false negatives were found in the BCLIP. If these results are confirmed in the definitive study, they would further improve the false-negative rate of 6.8% found in the ACOSOG Z1071 trial [11] and the 2% in the study by Caudle [12]. This would enable ALND to be omitted quite safely although, as mentioned, an analysis of recurrences and survival over at least 5 years would be necessary to ensure that such an omission does not increase recurrence or reduce survival in these patients.

Another factor worth noting is that when TAD (SLNB + BCLIP) is performed the results are identical to when BCLIP is done in isolation. However, in the study by Caudle [12] TAD improved the false-negative rate, from 4.2% to 2%, compared to when only BCLIP was done. SLNB is a very beneficial test for women with a clinically unaffected axilla (cN0) [26,27], but not so much when the axilla is positive. Moreover, taking into consideration the resource consumption, discomfort and radiation these patients receive with this isotopic test, further prospective studies should be conducted to clarify whether SLNB is really necessary in N-positive patients undergoing NACT and lymph-node marking.

This is a preliminary study, with obvious limitations: the sample size is small, as reflected in the high dispersion of data found, for which reason the results should be interpreted with caution. Moreover, it shows an interobserver variability, as 5 different surgeons performed the lymph-node biopsies. This latter limitation is difficult to overcome, but it may increase the possibilities of application and reproducibility in a real environment with departments made up of a variable number of surgeons with different experience and skills.

In conclusion, we can say from the preliminary results that TAD is a feasible and reproducible test for axillary restaging after NACT. It yields a high location rate and high NPV without false negatives, which means that patients with TAD would benefit from being spared ALND. The association of SLNB does not add diagnostic value in our sample, so it suggests that it could be omitted in this group of patients. We need a larger number of patients (at least 59) to confirm these results.

Authorship

Diego Flores-Funes: conception and design of the study, acquisition of data, analysis and interpretation of data, draft the article.

José Aguilar-Jiménez: conception and design of the study, analysis and interpretation of data, revise and correct the written article.

María Martínez-Gálvez: conception and design of the study, analysis and interpretation of data, revise and correct the written article.

María José Ibáñez-Ibáñez: conception and design of the study, acquisition of data, draft the article.

Luis Carrasco-González: analysis and interpretation of data, revise and correct the written article.

José Ignacio Gil-Izquierdo: analysis and interpretation of data revise and correct the written article.

María Asunción Chaves-Benito: analysis and interpretation of data, revise and correct the written article.

Francisco Ayala-De La Peña: analysis and interpretation of data,

Table 5
Sensitivity, specificity, positive and negative predictive values, false negative rate, positive and negative likelihood ratio, pre-test and post-test probability of SNLB, BCLIP and TAD, taking as Gold Standard the metastatic affectation in the ALND. SNLB: Sentinel Lymph Node Biopsy. BCLIP: Clipped Lymph Node Biopsy. TAD: Targered Axillary Dissection. ALND: Axillary Lymph Node Dissection.

	SNLB	BCLIP	TAD (SLNB + BCLIP)
Sensitivity	0.60 (0.07–1.0)	1.00 (0.59–1.00)	1.00 (0.59–1.00)
Specificity	0.79 (0.54–1.0)	0.73 (0.45–0.92)	0.73 (0.45–0.92)
Positive predictive value	0.5 (0.02–0.98)	0.64 (0.43–0.80)	0.64 (0.43–0.80)
Negative predictive value	0.85 (0.61–1.0)	1.00 (0.74–1.00)	1.00 (0.74–1.00)
False negative rate	0.15 (0.0–0.41)	0.0 (0.0–0.25)	0.0 (0.0–0.25)
Positive likelihood ratio	2.80 (0.82–9.60)	3.75 (1.62–8.68)	3.75 (1.62–8.68)
Negative likelihood ratio	0.51 (0.17–1.54)	0.00 (0.01–1.30)	0.00 (0.01–1.30)
Pre-test probability	0.26 (0.09–0.51)	0.32 (0.14–0.55)	0.32 (0.14–0.55)
Positive Post-test probability	0.50 (0.23–0.77)	0.64 (0.41–0.78)	0.64 (0.41–0.78)
Negative Post-test probability	0.15 (0.06–0.35)	0.00 (0.00–0.38)	0.00 (0.00–0.38)

revise and correct the written article.

Andrés Nieto-Olivares: analysis and interpretation of data revise and correct the written article.

José Luis Aguayo-Albasini: final approval of the version to be submitted.

Funding and conflicts of interest

The authors declare they have received no financial assistance and that there is no conflict of interests regarding the writing of this paper.

Acronyms

ALND	axillary lymph node dissection
BCLIP	clipped lymph-node biopsy
CI95%	95% confidence interval
FNA	fine needle aspiration
FNR	false-negative rate
FPR	false-positive rate
IQR	interquartile range
LR	location rate
NACT	neoadjuvant chemotherapy
NLR	negative likelihood ratio
NPV	negative predictive value
OSNA	one-step nucleic acid amplification
pCR	axillary complete response
PLR	positive likelihood ratio
PPV	positive predictive value
SLNB	sentinel lymph-node biopsy
TAD	targeted axillary dissection

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.05.019.

References

[1] K.G. Andersen, E.K. Aasvang, N. Kroman, H. Kehlet, Intercostobrachial nerve handling and pain after axillary lymph node dissection for breast cancer, Acta Anaesthesiol. Scand. 58 (10) (2014) 1240–1248.

[2] Y. Cho, J. Do, S. Jung, O. Kwon, J.Y. Jeon, Effects of a physical therapy program combined with manual lymphatic drainage on shoulder function, quality of life, lymphedema incidence, and pain in breast cancer patients with axillary web syndrome following axillary dissection, Support. Care Canc. 24 (5) (2016) 2047–2057.

[3] J. Boughey, V. Suman, E. Mittendorf, G. Ahrendt, L. Wilke, B. Taback, et al., Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the American college of surgeons Oncology group (ACOSOG) Z1071 clinical trial, J. Am. Med. Assoc. 310 (14) (2014) 1455–1461.

[4] S. Park, J.M. Park, J.H. Cho, H.S. Park, S Il Kim, B.-W. Park, Sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with cytologically proven node-positive breast cancer at diagnosis, Ann. Surg. Oncol. 20 (9) (2013) 2858–2865.

[5] V. Galimberti, S.K. Ribeiro Fontana, P. Maisonneuve, F. Steccanella, A.R. Vento, M. Intra, et al., Sentinel node biopsy after neoadjuvant treatment in breast cancer: Five-year follow-up of patients with clinically node-negative or node-positive disease before treatment, Eur. J. Surg. Oncol. 42 (3) (2016) 361–368.

[6] D. Carrera, M. de la Flor, J. Galera, K. Amillano, M. Gomez, V. Izquierdo, et al., Validación de la biopsia selectiva del ganglio centinela en mujeres con cáncer de mama N1-2 con respuesta axilar completa tras la neoadyuvancia. Estudio multicéntrico en la provincia de Tarragona, Rev. Española Med. Nucl. Imagen Mol. 35 (4) (2016) 221–225.

[7] L. Zetterlund, F. Celebioglu, R. Axelsson, J. de Boniface, J. Frisell, Swedish prospective multicenter trial on the accuracy and clinical relevance of sentinel lymph node biopsy before neoadjuvant systemic therapy in breast cancer, Breast Canc. Res. Treat. 163 (1) (2017) 93–101.

[8] R. Alvarado, M. Yi, H. Le-Petross, M. Gilcrease, E.A. Mittendorf, I. Bedrosian, et al., The role for sentinel lymph node dissection after neoadjuvant chemotherapy in patients who present with node-positive breast cancer, Ann. Surg. Oncol. 19 (10) (2012) 3177–3184.

[9] T. Kuehn, I. Bauerfeind, T. Fehm, B. Fleige, M. Hausschild, G. Helms, et al., Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study, Lancet Oncol. 14 (7) (2013) 609–618.

[10] K. Enokido, C. Watanabe, S. Nakamura, A. Ogiya, T. Osako, F. Akiyama, et al., Sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with an initial diagnosis of cytology-proven lymph node-positive breast cancer, Clin. Breast Canc. 16 (4) (2016) 299–304.

[11] J.C. Boughey, K.V. Ballman, H.T. Le-Petross, L.M. McCall, E.A. Mittendorf, G.M. Ahrendt, 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), Ann. Surg. 263 (4) (2016) 802–807.

[12] A.S. Caudle, W.T. Yang, S. Krishnamurthy, E.A. Mittendorf, D.M. Black, M.Z. Gilcrease, 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. 34 (10) (2016) 1072–1078.

[13] E.Y. Kim, W.S. Byon, K.H. Lee, J.S. Yun, Y.L. Park, C.H. Park, 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. 42 (2) (2018) 582–589.

[14] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (2) (2009) 228–247.

[15] W.F. Symmans, F. Peintinger, C. Hatzis, R. Rajan, H. Kuerer, V. Valero, et al., Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy, J. Clin. Oncol. 25 (28) (2007) 4414–4422.

[16] S.B. Edge, C.C. Compton, The American Joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the Future of TNM, Ann. Surg. Oncol. 17 (6) (2010) 1471–1474.

[17] H.J. Bloom, W.W. Richardson, Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years, Br. J. Canc. 11 (3) (1957) 359–377.

[18] Inicio, Consellería de Sanidade - SERGAS, [cited 2017 Jan 16]. Available from http://www.sergas.es/.

[19] P.M. Bossuyt, J.B. Reitsma, D.E. Bruns, C.A. Gatsonis, P.P. Glasziou, L. Irwig, et al., STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies, BMJ (2015) h5527.

[20] J.M. Chang, H.E. Kosiorek, N. Wasif, R.J. Gray, C.C.H. Stucky, D.W. Northfelt, et al., The success of sentinel lymph node biopsy after neoadjuvant therapy: a single institution review, Am. J. Surg. 214 (6) (2017) 1096–1101.

[21] O. Kantor, L.M. Sipsy, K. Yao, T.A. James, A predictive model for axillary node pathologic complete response after neoadjuvant chemotherapy for breast cancer, Ann. Surg. Oncol. 25 (5) (2018) 1304–1311.

[22] E. Avisar, T. Ozmen, Management of the positive axilla in 2017, Breast Canc. Res. Treat. 163 (3) (2017) 413–415.

[23] D. Plecha, S. Bai, H. Patterson, C. Thompson, R. Shenk, Improving the accuracy of axillary lymph node surgery in breast cancer with ultrasound-guided wire localization of biopsy proven metastatic lymph nodes, Ann. Surg. Oncol. 22 (13) (2015) 4241–4246.

[24] C. Siso, J. de Torres, A. Esgueva-Colmenarejo, M. Espinosa-Bravo, N. Rus, O. Cordoba, 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. 25 (3) (2018) 784–791.

[25] Y.E. Ersoy, H. Kadioglu, Review of novel sentinel lymph node biopsy techniques in breast cancer patients treated with neoadjuvant chemotherapy, Clin. Breast Canc. (2018) 1–5.

[26] N. Bromham, M. Schmidt-Hansen, M. Astin, E. Hasler, M.W. Reed, Axillary treatment for operable primary breast cancer, Cochrane Database Syst. Rev. 1 (2017) CD004561.

[27] P. Charalampoudis, C. Markopoulos, T. Kovacs, Controversies and recommendations regarding sentinel lymph node biopsy in primary breast cancer: a comprehensive review of current data, Eur. J. Surg. Oncol. 44 (1) (2018) 5–14.