CIRUGÍA ESPAÑOLA

Original article

Lymph node staging after primary systemic therapy in women with breast cancer and lymph node involvement at diagnosis☆

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ARTICLE INFO

ABSTRACT

Objective: The main objective of this study is to analyze the efficacy of combined axillary marking (lymph node clipping and sentinel lymph node biopsy (SLNB)) for axillary staging in patients with primary systemic treatment (PST) and pathologically confirmed node-positive breast cancer at diagnosis. The secondary objective is to determine the impact of lymph node marking in the suppression of axillary lymph node dissection (ALND) in the study group.

Methods: We conducted a prospective study in which lymph node staging was performed using wire localization of positive lymph nodes and a SLNB with dual tracer. All patients who presented no metastatic involvement of the sentinel lymph node (SLN) or clip/wire-marked lymph node were spared an ALND. The multidisciplinary committee agreed on axillary treatment for patients with lymph node involvement. Results: Eighty one patients met the inclusion criteria. We identified and extirpated the clip/ wire-marked node in 80 of 81 patients (98.8%), with SLNB performed successfully in 88,9% of patients. The SLN and wire-marked node matched in 78.9% of patients; 76.2% of patients did not undergo ALND.

Conclusions: The combined axillary marking (clip and SLNB) in patients with metastatic lymph node at diagnosis and PST offers a high identification rate (98.8%) and a high correlation between the wire-marked lymph node and the SLN (78.9%). This procedure has enabled the suppression of ALND in 76.2% of patients.

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Estadificación ganglionar tras terapia sistémica primaria en mujeres con cáncer de mama y afectación ganglionar al diagnóstico

R E S U M E N

Palabras clave:
Terapia sistémica primaria
Estadificación ganglionar
Disección axilar dirigida

Objetivo: El objetivo principal de este estudio es analizar la eficacia del marcaje ganglionar combinado (clip y biopsia de ganglio centinela (BGC)) para la estadificación axilar en pacientes con tratamiento sistémico primario (TSP) y cáncer de mama con ganglios positivos confirmados patológicamente en el momento del diagnóstico. El objetivo secundario es determinar el impacto del marcaje ganglionar en la supresión de la linfadenectomía axilar (LA) en el grupo a estudio.

Métodos: Estudio prospectivo en el que se realizó la estadificación ganglionar mediante la localización con alambre metálico (arpón) de los ganglios afectados y una BGC con doble trazador. Todas las pacientes sin afectación metastásica del ganglio centinela (GC) o del ganglio marcado con clip/alambre no realizaron una LA. El comité multidisciplinar acordó el tratamiento axilar de las pacientes con afectación ganglionar.

Resultados: Ochenta y un pacientes cumplieron los criterios de inclusión. Identificamos y extirpamos el ganglio marcado con clip/alambre en 80 de 81 pacientes (98,8%), y la BGC se realizó con éxito en el 88,9% de los pacientes. El GC y el nódulo marcado con arpón coincidieron en el 78,9% de las pacientes. El 76,2% de las pacientes no se sometieron a LA.

Conclusiones: el marcaje axilar combinado (clip y BGC) en pacientes con ganglios metastásicos al diagnóstico y TSP ofrece una alta tasa de identificación (98,8%) y una alta correlación entre el ganglio marcado con arpón y el GC (78,8%). Este procedimiento ha permitido la supresión de la LA en el 76,2% de las pacientes incluidas en el estudio.

Introduction

Sentinel node biopsy (SNB) is the procedure of choice for axillary staging in patients with breast cancer and primary surgery, as several studies have shown that overall survival (OS) and disease-free survival (DFS) is similar in patients undergoing SNB and cambiar axillary lymphadenectomy por axillary lymph node dissection (ALND) when the sentinel node (SN) is negative.[1,2] The ACOSOG-Z0011[3] and AMAROS[4] studies later demonstrated that omitting AL in patients with SN involvement offered similar survival to AL using whole breast and/or axillary irradiation. In contrast, after primary systemic treatment (PST), AL has been the technique of choice in patients with lymph node involvement at diagnosis or lymph node metastasis after PST.

There is currently controversy regarding the ideal axillary staging technique after PST in women with lymph node involvement at diagnosis. Several groups[5,6] propose assessing nodal response after PST to avoid AL in patients with pathological complete response (pCR). In recent years, a new staging technique called targeted axillary dissection (TAD)[7] has been proposed to reduce the indication for AL in this group of patients.

The primary objective of this study is to analyse the efficacy of combined lymph node marking (clip and SNB) for axillary staging in patients with PST and breast cancer with metastatic lymph node involvement at diagnosis. The secondary objective is to determine the impact of lymph node marking on avoiding AL in the study group.

Methodology

A prospective non-randomised study from our centre's breast unit between May 2016 and January 2022. The study included women over 18 years of age with breast cancer (all histological types and tumour subtypes, except sarcomas) and axillary node involvement at diagnosis (N1) who received PST on the recommendation of the multidisciplinary committee, based on international clinical guidelines.[8–10] Patients with distant metastases at diagnosis (M1), clinical or radiological progression of disease during PST, four or more nodes suspicious for malignancy at diagnosis, and patients who chose not to participate in the study were excluded (Table 1). The study was approved by the Autonomous Research Ethics Committee (Promoter Code: SENTINA 00-14; Registration Code: 2014/140).

Radiological method

An axillary ultrasound was performed for lymph node staging prior to PST. Each lymph node was classified based on morphological features of the cortical and hilum lymph nodes using the Bedi et al.[11] classification and nodes with a Bedi category 4–6 were biopsied and clip marked. In patients with more than 1 suspicious node, the node with the highest suspicion of metastatic involvement was biopsied and marked. Once the PST had been completed, the clip-marked lymph node was marked with a metal guide (harpoon) during diagnosis. Likewise, the SN was marked by isotope mapping

Table 1 – Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
- Females - Over the age of 18 years - Infiltrating breast carcinoma (all histological types, except sarcomas) - All tumour subtypes (by IHC) - Lymph node involvement at diagnosis (cN1) - Indication for primary systemic therapy - Agreeing to participate in the study - Pathological confirmation of lymph node involvement (SNB) - Biopsied lymph node marking	- Males - Under the age of 18 years - Breast sarcomas - No lymph node involvement at diagnosis (cN0) - Involvement of more than 4 lymph nodes at diagnosis (cN2-3) - Distant metastasis at diagnosis - Progression during primary systemic therapy - Refusing to take part in the study - Lack of histological confirmation of nodal metastasis - No biopsied lymph node marking

with technetium-99 in the periareolar region. If no radioisotope uptake was evident, the SN mapping was complemented with patent blue. All patients underwent a breast MRI prior to starting PST and another when PST had finished to determine the degree of response in the breast and axilla.

Primary systemic therapy

All the patients included in the study underwent PST according to the clinical guidelines for each period.[9,10] All the patients were treated with four cycles of adriamycin and cyclophosphamide, and 12 cycles of paclitaxel. The medical oncologist decided the sequence of these therapies. All the women who were HER2 receptor positive were treated with monoclonal antibodies (trastuzumab with or without pertuzumab).

Surgical method

All the patients included in the study underwent surgery after completing the selected neoadjuvant chemotherapy regimen. On the day of surgery, the clip-marked lymph node was removed. Once this node was removed, it was checked for isotopic load and/or patent blue staining. The presence of the clip in the marked lymph node was confirmed by X-ray of the sample. Finally, a complementary axillary examination was conducted to check for the presence of other radioisotope/dye-marked SN. We defined as an SN those with an isotope count ten times higher than baseline and/or those stained with patent blue or with a blue lymphatic duct. Non-sentinel nodes were defined as those suspicious on palpation, those that did not show blue dye, nodes without radiotracer activity. The surgery report specified whether the SN coincided with the clip-marked node.

In the patients who underwent mastectomy, an intraoperative study of the removed nodes was performed using the OSNA method. In case of macrometastatic lymph node involvement, AL was performed in the same surgical procedure. A delayed lymph node study was performed in the patients who underwent breast-conserving surgery. If this study showed metastatic lymph node involvement, the case was discussed in the multidisciplinary breast committee to assess the indication for AL. The multidisciplinary committee is made up of medical oncologists, radiation oncologists, breast surgeons, breast radiologists, and pathologists. The individual characteristics of each patient were assessed (number of affected nodes, tumour biology, response to PST in the breast, associated morbidities, etc.). The committee agreed to omit AL in women with any favourable characteristics such as complete pathological response in the breast, removal of more than one node and one without disease, and/or micrometastasis of the node. In patients undergoing AL, Berg levels I and II were removed, and only level III was removed in the patients with macroscopic involvement of this level. Radiotherapy of lymph node chains was indicated in cases where the committee recommended omitting AL.

Micrometastases were defined as tumour inclusions between 0.2 and 2 mm, equivalent in the OSNA method to a copy number between 250 and 5000. Macrometastases are metastases >2 mm or more than 5000 copies by OSNA. Finally, isolated tumour cells are metastases smaller than 0.2 mm and correspond to <250 copies by OSNA assay.

Indication and planning of radiotherapy treatment

All the breast-conserving surgery patients included in the study received breast radiotherapy between the fourth and sixth week after surgery. Breast irradiation was performed using tangential fields at a dose of 50 Gy in 25 fractions of 2 Gy, 5 times per week. In case with over-impression of the tumour bed, additional doses of 8−10 Gy were given, spread over 4 or 5 sessions. In all the women undergoing mastectomy, chest wall radiotherapy was indicated at doses of 45−50 Gy in 25 fractions of 1.8−2 Gy/day to the chest wall. Patients with an indication for radiotherapy of lymph node chains received doses of 50 Gy in 25 sessions, with a depth of 3 cm.

Statistical method

We used IBP SPSS Statistics version 22 (IBM Corporation, Armonk, NY, USA) for data collection and analysis. Quantitative variables are listed with their mean and standard deviation and qualitative variables are listed with their proportions. Differences between qualitative variables will be found by Fisher's exact test or $\chi 2$ test. Kaplan-Meier curves were used to perform the OS study.

Results

The study group consisted of 81 patients with infiltrating breast carcinoma and metastatic involvement of the axilla at diagnosis treated with PST. The most frequent tumour subtype was luminal B Her2 negative (32.1%) followed by luminal B Her2 positive (27.2%).

Series characteristics. The mean initial tumour size was 3.6 cm (±1.5) and the mean final tumour size 0.7 cm (±1.1)

Table 2 – Clinical and pathological characteristics of the patients.

	Patients n = 81
Age (years)	
Mean	53.3 (±11.5)
Range	26−81
Tumour subtype	
Luminal A	2 (2.5%)
Luminal B Her2-	26 (32.1%)
Luminal B Her2+	22 (27.2%)
Her2+	13 (16.0%)
Triple negative	18 (22.2%)
SN marking	
Technetium	41 (50.6%)
Patent blue	5 (6.2%)
Blue + Technetium	35 (43.2%)
Initial tumour size (cm)	
Mean	3.6 (±1.5)
Range	1.2–8.4
Initial tumour size (cTNM)	
T1c	9 (11.1%)
T2	57 (70.4%)
T3	15 (18.5%)
Final tumour size (cm)	
Mean	0.7 (±1.1)
Range	0–6

Surgical results	Patients n = 81
Type of breast surgery	
Lumpectomy	54 (66.7%)
Oncoplasty	8 (9.9%)
Mastectomy	19 (23.5%)
pCR in breast	35 (43.2%)
pCR in breast according to tumour subtype	
Luminal A	0/2 (0%)
Luminal B Her2−	5/26 (19.2%)
Luminal B Her2+	11/22 (50%)
Her2+	12/18 (66.7%)
Triple negative	7/13 (53.8%)
Excised SN	2,6 (±1.5)
Patients with axillary involvement after chemotherapy	36 (44.4%)
Axillary lymph node dissection	19 (23.5%)
SN excised in the lymphadenectomy	12.6 (±5.9)
	3−27
Type of axillary involvement	
ypN0	45 (55.6%)
ypN1mi	14 (17.3%)
ypN1	22 (27.2%)
pCR in the marked SN/lymph node	
Luminal A	0/2 (0.0%)
Luminal B Her2−	6/26 (23.1%)
Luminal B Her2+	15/22 (68.2%)
Her2+	15/18 (83.3%)
Triple negative	9/18 (69.2%)
Axillary response according to breast response (complete or partial)	
Luminal A	0/0 (0.0%)
Luminal B Her2−	3/5 (60.0%)
Luminal B Her2+	10/11 (90.9%)
Her2+	11/12 (91.7%)
Triple negative	6/7 (85.7%)

SN, sentinel node; pCR, partial complete response.

Table 3 – Identification and concordance of axillary marking.

	Patients n = 81
Identification of clip and wire placement	81 (100%)
Excision of wire-marked lymph node	80 (98.8%)
Sentinel gland biopsy	72 (88.9%)
Concordance between clip-marked node and sentinel node	56/71 (78.9%)
Ability of the marked lymph node to detect axillary involvement	32/36 (88.9%

(Table 2). The breast was conserved in 76.6% of the patients (lumpectomy 66.7% and oncoplasty 9.9%) (Table 3). Of the patients with a pCR in the breast, 85.7% also had a pCR in the axilla (ypN0). In contrast, only 34% of patients with a partial response in the breast were negative for lymph node disease. Axillary response was statistically superior in tumours with Her2 overexpression and response in the breast. Thus, 91.7% of pure Her2 tumours and 90.9% of Her2-positive luminal B tumours with pCR in the breast, were negative in the axilla (p = 0.001). Two patients with Her2-negative luminal B tumours that did not respond to PST had residual axillary disease.

Axillary treatment. Of the patients included in the study, 85.2% (69) had metastatic involvement of only 1 node; 4 women (4.9%) had 2 nodes suspicious for metastatic involvement, and 8 patients (9.9%) had 3 nodes. The axillary marking clip was detected by ultrasound in all the patients in the study group, which allowed wire placement in all patients (Table 4). The clip/wire-marked lymph node was removed in 80 of 81 patients (98.8%), while isotope/dye-marking identified the SN in 72 patients (88.9%). This SN was the same as the clip-marked node in 56 patients (78.9%).

A total of 45 patients (55.6%) had a complete response in the axilla after PST. With these pathological findings the breast committee recommended AL in 18 patients (23.5%) (Fig. 1):

- **ypN0**. An AL was not performed in 97.8% of the patients with axillary response (44 out of 45 women). One of the 45 patients without involvement of the marked lymph node underwent axillary AL, as no SN was detected, and the axilla appeared macroscopically affected. Seven of these patients in whom AL was avoided (8.6%) did not receive axillary radiotherapy either (Fig. 1).
- **ypN1**. An AL was not performed in 50% of the patients with persistent metastatic lymph node involvement. Of these patients, 66.7% (12 of 18) had micrometastatic lymph node involvement and all received axillary radiotherapy. Five of the 6 patients with macrometastases (83.3%), without axillary AL, had other sentinel nodes without disease.

Oncological events. The mean follow-up time was 24.2 ± 16 months (range: 1.3–68.5) and no axillary relapses were detected during follow-up. One patient who underwent AL and lymph node radiotherapy died 47 months after

Table 4 – Axillary treatment according to lymph node involvement.

	Without axillary treatment	Axillary lymph node dissection	Axillary lymph node dissection	Axillary lymph node dissection + radiotherapy
ypN0	7 (8.6%)	0 (0%)	37 (45.7%)	1 (1.2%)
ypN1mi	0 (0%)	0 (0%)	12 (14.8%)	2 (2.5%)
ypN1	0 (0%)	0 (0%)	6 (7.4%)	16 (19.8%)

SLNB/MN: Sentinel lymph node biopsy/marked node
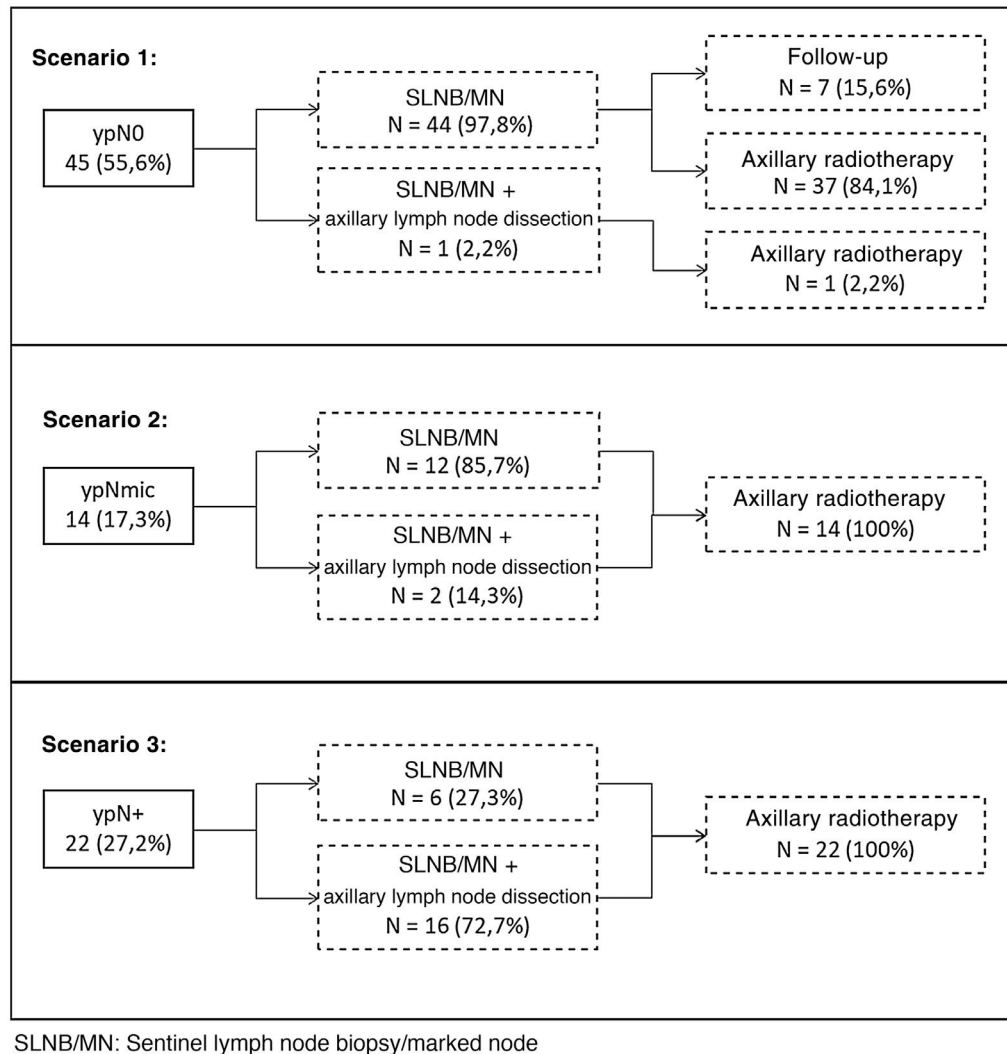
Fig. 1 – Axillary treatment.

surgery due to metastatic progression of her breast cancer, resulting in an OS at 48 months of 88.9% (95%CI 78.4%–99.4%) (Fig. 2).

Discussion

Axillary surgery in women with breast cancer has been de-escalated in recent years. However, axillary surgery after PST has not been shown to be similarly less intensively performed, due to the absence of prospective studies evaluating these women. This study analyses the efficacy of clip marking the affected lymph node after PST. This efficacy depends on the method used for marking and therefore several studies have evaluated these methods. Donker et al.[12] marked the axillary node with radioactive iodine (125I) seeds (MARI procedure) with an identification rate of 97% and an FN rate of 7%. Caudle et al.[7] used the TAD method to evaluate the response of
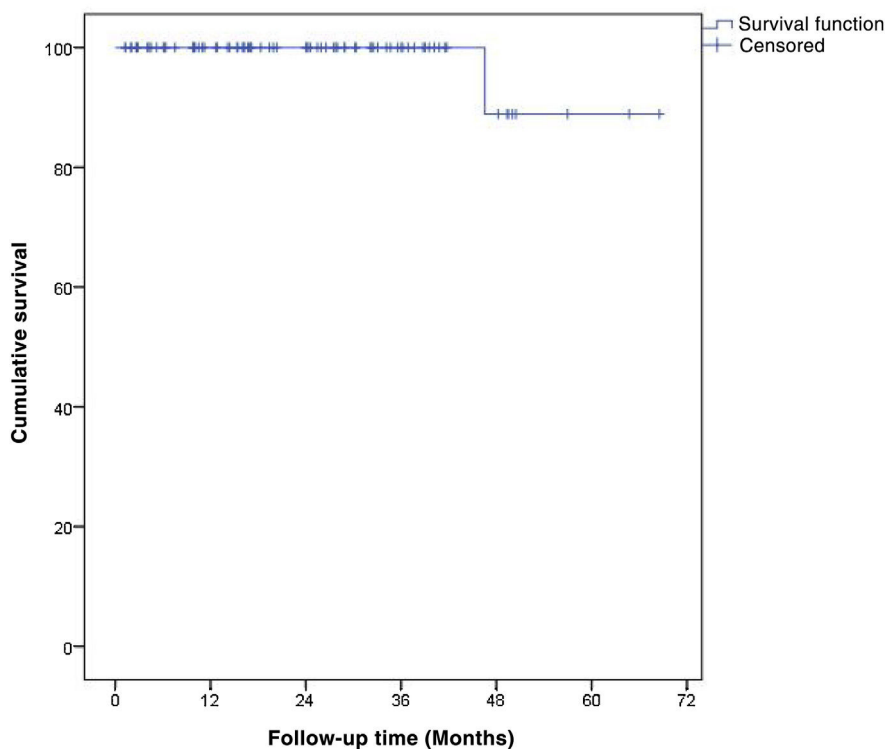
Fig. 2 – Overall survival of study group.

metastatic axillary nodes to PST. The identification rate achieved by this group was 95%, with an FN rate of 2%. In contrast, when only the marked node or the SN was removed, the FN rate was 4.2% and 10.1%, respectively. Boughey et al.[13] demonstrated in the ACOSOG Z1071 study that placing a clip on the affected node during diagnosis of the disease combined with SNB is an appropriate method to decrease the FN rate. This rate decreased from 19.9% to 6.8% in patients with SNB and selective marking of the biopsied node, respectively. The retrospective study by Simons et al.[14] used radioactive iodine seeds to identify the biopsied lymph node after PST combined with SNB, obtaining an identification rate of 92.8% and an FN rate of 2%–4% combining both procedures. Hellingman et al.[15] later proposed a modification of the MARI procedure by injecting technetium-99m-labelled macroaggregated albumin into the clip-marked nodes and then removing it during surgery, achieving an identification rate of 87%. Recently the study by Martínez et al.[16] evaluated the safety and efficacy of magnetic seeds as a method of axillary staging, obtaining an identification rate of 100% and a reduction in FN rate from 21.4% to 5.9% when combined with SNB and removal of the marked node. The study by Siso et al.[17] used ultrasound to identify the clip-marked lymph node with an identification rate of 95.4% and an FN rate of 4.1%. Gurleyik et al.[18] achieved an identification rate of 98.4% using ultrasound-guided lymph node localisation after PST. The studies by Park et al.[19] and Patel et al.[20] analysed the efficacy of lymph node tattooing with charcoal and black ink respectively, obtaining an FN rate

of 20.0% and 13.3%. In our study, the clip was detected in 100% of patients. Wire marking identified the marked node in 80 out of 81 patients (98.8%) and isotope/dye marking identified the SN in 72 patients (88.9%). Other authors have employed a similar methodology to ours using a guidewire. Plecha et al.[21] and Hartmann et al. [22] obtained mixed results. However, the study by Plecha et al.[21] achieved a 97.3% success rate for the procedure, affirming that the wire-guided localisation of metastatic axillary nodes is an accurate technique and that it improves FN and surgical removal rates. In contrast, the study by Hartmann et al.[22] obtained an identification rate of 70.8%, stating that this technique is not suitable for routine clinical practice. These discrepancies could be due to differences in the experience of the surgeons/radiologists participating in the study. In our opinion, this staging procedure is an efficient and easily reproducible method, as it uses the same methodology as that used for non-palpable breast lesions, thus making it a method that can be extrapolated to most breast units. In addition, it does not require investment and does not entail the radiological safety risks associated with other techniques.

The second objective of the study was to determine the decrease in AL according to the type of pathological response after PST in the biopsied lymph node. In our experience, the tumour profiles with the highest incidence of pCR were Her2-positive and triple-negative tumours, with responses of 91.7% and 85.7%, respectively. Comparable results were obtained in the studies of Samiei et al.[23] and Gurleyik et al.,[18] and in all the

studies the rates of breast-conserving surgery were significantly higher in Her2-positive and triple-negative tumours. These results raise the possibility of de-escalating axillary surgery in patients with a marked lymph node pCR in a manner similar to planning in the breast after a pCR. Two factors would support this approach. The first relates to the use of breast and axillary radiotherapy in this group of women with nodal involvement at diagnosis, which guarantees oncological safety after breast and axillary node preservation. Secondly, studies such as that of Fayanju et al.[24] show that the group of patients with lymph node pCR have a comparable prognosis to patients with clinically negative nodes at diagnosis.

In our study a total of 56 patients (78.9%) had concordance between the two markers, an incidence similar to that found in other studies (75.9%–77%).[7,13,17] This high concordance between the marked lymph node and the SN suggests that they are the same node, which would be in line with the definition of the SN as the node most likely to metastasise.[25] In these patients the disease itself will have marked their SN, which could suggest omitting SNB in these patients. In contrast, other studies have shown lower concordance rates, with values ranging from 35.7% to 65%.[16,22,26] Also in this study, 21.1% of patients had no concordance between the marked node and the SN. These discrepancies may be due to lymphatic blockage and less likely, to an error in marking the biopsied node. Therefore, we believe that patient selection for lymph node staging after PST is significant, which in our study focused on women with limited involvement of the axilla (N1).

In our experience, 61 patients (76.3%) were spared AL, and the group with lymph node pCR benefitted the most. However, in 50% of patients with persistent metastatic lymph node involvement, despite the recommendation of the clinical guidelines, omission of AL was indicated after individual assessment by the tumour committee and inclusion in this prospective study. A study by Nijnatten et al.[27] compares DFS and OS among patients with lymph node-positive breast cancer at diagnosis based on their response to neoadjuvant chemotherapy. The results of this study conclude that there is no significant difference between patients with axillary pCR (ypN0) and patients with isolated tumour cells (ypN0itc) or micrometastases (ypN1mi). In contrast, residual axillary macrometastases (ypN1) were associated with a less favourable prognosis. The multicentre study by Cabioglu et al.[28] showed similar results, stating that AL could be avoided in patients with breast and/or lymph node pCR after neoadjuvant chemotherapy and in the case of cT1-2 or low tumour load (micrometastases or isolated tumour cells) lymph node residue in luminal subtypes, provided that axillary radiotherapy is given. In contrast, studies by Wong et al.[29] and Fisher et al.[30] argue that low-volume residual disease after neoadjuvant chemotherapy is associated with lower DFS, and OS rates compared to those with negative nodes. These discrepancies call for prospective studies to assess the impact of AL and axillary radiotherapy on the mid- and long-term outcomes of patients with macrometastases after PST. In our study, no axillary relapses were recorded during follow-up in patients who did not undergo AL and were treated with axillary radiotherapy, but further follow-up is needed to assess the

oncological safety of this surgical de-escalation, especially in women with macrometastases after PST.

Our study has several limitations. The absence of AL in a significant group of patients prevents us from knowing the FN rate of the series. A second limitation is the short follow-up time (mean follow-up of 24 months), which prevents us from making a correct assessment of oncological safety and the impact on overall survival of the procedure in the medium term, especially in the patients in whom AL was avoided.

In conclusion, our study shows that combined axillary marking (clip in the biopsied lymph node and SNB) has a high efficacy rate for nodal staging (98.8%). Of these marked lymph nodes, 78.9% were consistent with the SN. Patients with Her2 and triple negative tumours have a high rate of pCR (91.7% and 85.7% respectively) and therefore constitute a group for whom this procedure is specially indicated. In our study, AL was avoided in 76.25% of the women, and therefore we consider that the effort involved in marking and removing the biopsied lymph node is justified.

Financing

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T, et al. Technical outcomes of sentinel-lymphnode resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: Results from the NSABP B-32 randomised phase III trial. Lancet Oncol. 2007;8:881–8.

2. Gentilini O, Veronesi U. Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: Sentinel node vs observation after axillary UltraSouND) Breast. 2012;21:678–81. http://dx.doi.org/10.1016/j.breast.2012.06.013.

3. Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 randomized trial. Ann Surg. 2016;264:413–20. http://dx.doi.org/10.1097/SLA.0000000000001863.

4. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, openlabel, phase 3 non-inferiority trial. Lancet Oncol. 2014;15:1303–10.

5. Boileau JF, Poirier B, Basik M, Holloway CMB, Gaboury L, Sideris L, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node positive breast cancer:

the SN FNAC study. J Clin Oncol. 2015;33(3):258–64. http://dx.doi.org/10.1200/jco.2014.55.78275.

6. 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. JAMA. 2013;310(14):1455–61.

7. 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. J Clin Oncol. 2016;34(10):1072–8. http://dx.doi.org/10.1200/jco.2015.64.0094.

8. Bedi DG, Krishnamurthy R, Krishnamurthy S, Edeiken BS, LePetross H, Fornage BD, 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. http://dx.doi.org/10.2214/ajr.07.2460.

9. NCCN Clinical Practice Guidelines in Oncology. Version 2.2019. National Comprehensive Cancer Network. Consultado por última vez: marzo 2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf.

10. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(8):1194–220. http://dx.doi.org/10.1093/annonc/mdz189.

11. Bedi DG, Krishnamurthy R, Krishnamurthy S, Edeiken BS, Le-Petross H, Fornage BD, 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. http://dx.doi.org/10.2214/AJR.07.2460.

12. 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. Ann Surg. 2015;261(2):378–82. http://dx.doi.org/10.1097/sla.0000000000000558.

13. Boughey JC, Ballman KV, Le-Petross HT, McCall LM, Mittendorf EA, Ahrendt GM, et al. Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer (T0-T4, N1-N2) who receive neoadjuvant chemotherapy: results from ACOSOG Z1071 (Alliance). Ann Surg. 2016;263(4):802–7. http://dx.doi.org/10.1097/sla.0000000000001375.

14. Simons JM, van Nijnatten TJA, van der Pol CC, Luiten EJT, Koppert LB, Smidt ML. Diagnostic accuracy of different surgical procedures for axillary staging after neoadjuvant systemic therapy in node-positive breast cancer: a systematic review and meta-analysis. Ann Surg. 2019;269(3):432–42.

15. Hellingman D, Donswijk ML, Winter-Warnars GAO, de Koekkoek-Doll P, Pinas M, Budde-van Namen Y, et al. Feasibility of radioguided occult lesion localization of clip-marked lymph nodes for tailored axillary treatment in breast cancer patients treated with neoadjuvant systemic therapy. EJNMMI Res. 2019;9(1):94. http://dx.doi.org/10.1186/s13550-019-0560-3.

16. Mariscal Martínez A, Vives Roselló I, Salazar Gómez A, Catanese A, Pérez Molina M, Solà Suarez M, 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. http://dx.doi.org/10.1016/j.suronc.2020.11.013.

17. Siso C, de Torres J, Esqueva-Colmenarejo A, Espinosa-Bravo M, Rus N, Cordoba O, 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. http://dx.doi.org/10.1245/s10434-017-6270-z.

18. Gurleyik G, Aksu SA, Aker F, Tekyol KK, Tanrikulu E, Gurleyik E. Targeted axillary biopsy and sentinel lymph node biopsy for axillary restaging after neoadjuvant chemotherapy. Ann Surg Treat Res. 2021;100(6):305–12. http://dx.doi.org/10.4174/astr.2021.100.6.305.

19. Park S, Koo JS, Kim GM, Sohn J, Kim SI, Cho YU, et al. Feasibility of charcoal tattooing of cytology-proven metastatic axillary lymph node at diagnosis and sentinel lymph node biopsy after neoadjuvant chemotherapy in breast cancer patients. Cancer Res Treat. 2018;50(3):801–12.

20. Patel R, MacKerricher W, Tsai J, Choy N, Lipson J, Ikeda D, et al. Pretreatment tattoo marking of suspicious axillary lymph nodes: reliability and correlation with sentinel lymph node. Ann Surg Oncol. 2019;26:2452–8. http://dx.doi.org/10.1245/s10434-019-07419-3.

21. Plecha D, Bai S, Patterson H, Thompson C, Shenk R. 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. 2015;22(13):4241–6. http://dx.doi.org/10.1245/s10434-015-4527-y.

22. Hartmann S, Reimer T, Gerber B, Stubert J, Stengel B, Stachs A, et al. 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. http://dx.doi.org/10.1016/j.ejso.2018.05.035.

23. Samiei S, van Nijnatten TJA, Munck L, Keymeulen KBMI, Simons JM, Kooreman LFS, et al. Correlation between pathologic complete response in the breast and absence of axillary lymph node metastases after neoadjuvant systemic therapy. Ann Surg. 2020;271(3):574–80.

24. Fayanju OM, Ren Y, Thomas SM, Greenup RA, Plichta JK, Rosenberger LH, et al. The clinical significance of breast-only and node-only pathologic complete response (pCR) after neoadjuvant chemotherapy (NACT): a review of 20,000 breast cancer patients in the national cancer data base (NCDB). Ann Surg. 2018;268(4):591–601.

25. Tanis PJ, Nieweg OE, Valdés Olmos RA, Th Rutgers EJ, Kroon BB. History of sentinel node and validation of the technique. Breast Cancer Res. 2001;3(2):109–12.

26. Simons JM, van Pelt MLMA, Marinelli AWKS, Straver ME, Zeillemaker AM, Pereira Arias-Bouda LM, et al. Excision of both pretreatment marked positive nodes and sentinel nodes improves axillary staging after neoadjuvant systemic therapy in breast cancer. Br J Surg. 2019;106(12):1632–9. http://dx.doi.org/10.1002/bjs.11320.

27. van Nijnatten TJA, Simons JM, Moossdorff M, de Munck L, Lobbes MBI, van der Pol CC, et al. Prognosis of residual axillary disease after neoadjuvant chemotherapy in clinically node-positive breast cancer patients: isolated tumor cells and micrometastases carry a better prognosis than macrometastases. Breast Cancer Res Treat. 2017;163(1):159–66. http://dx.doi.org/10.1007/s10549-017-4157-0.

28. Cabioğlu N, Karanlĭk H, Yĭldĭřĭm N, Müslümanoğlu M, Çakmak Karadeniz G, Trabulus Can D, et al. Favorable outcome with sentinel lymph node biopsy alone after neoadjuvant chemotherapy in clinically node positive breast cancer at diagnosis: Turkish Multicentric NEOSENTI-

TURK MF-18-02-study. Eur J Surg Oncol. 2021;47(10):2506–14. http://dx.doi.org/10.1016/j.ejso.2021.06.024.

29. Wong SM, Almana N, Choi J, Hu J, Gagnon H, Natsuhara K, et al. Prognostic significance of residual axillary nodal micrometastases and isolated tumor cells after neoadjuvant chemotherapy for breast cancer. Ann Surg Oncol.

2019;26(11):3502–9. http://dx.doi.org/10.1245/s10434-019-07517-2.

30. Fisher ER. Pathobiology of preoperative chemotherapy: findings from de National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. Cancer. 2002;95(4):681–95.