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Avoiding axillary lymphadenectomy in n+ triple-negative, her2-positive breast cancer after neoadjuvant chemotherapy

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Abstract: To evaluate the omission of the axillary lymphadenectomy in patients with N1 breast cancer negative triple and HER2-positive who showed an axillary response after neoadjuvant chemotherapy, and identify the axillary response in relation to the molecular subtypes. It is a description of the technique and the presentation of our experience. Method: A descriptive, retrospective study of 100 patients with cT1-T3/N1/M0 stage who received primary systemic therapy between January 2020 and January 2024; 72 of them received chemotherapy and/or anti-HER2 therapy and 28 hormonal therapies; biopsy and marking of the suspicious lymph node with nitinolÒ clips (maximum 3) was performed. In the surgery, a harpoon was placed in the axillary node + BSGC with 99mTc and methylene blue. Results: An axillary response was achieved in 52/100 cases (52 %), in 34/52 (65.3 %) it was a complete pathological response pCR and in 18/52 isolated tumor cells or micro metastases. Macrometastasis was observed in 48/100 (48 %) and therefore axillar lymphadenectomy (33) or axillary radiation therapy (15) was performed. The axillary response occurred in: Luminal A: 26 %, Luminal B: 42 %, HER2-positive 87 % and triple negative 77 %. The mean lymph node was 3.05. Conclusions: The 52 % of the cohort had an axillary response, thus avoiding the lymphadenectomy. Luminal A is scarce, the intention to negativize the armpit is controversial. The target axillary dissection is an oncological safe procedure; not less than the axillar lymphadenectomy.

Key words: cancer; breast; neoadjuvant; chemotherapy; target axillary dissection; primary systemic treatment

1 Introduction

Breast cancer (BC) is the most common malignancy worldwide, with more than 2,260,000 new cases annually [1]. If approximately 10% of BC cases present with axillary involvement, it could be inferred that there are about 250,000 BC cases with positive axillae, amenable to primary systemic therapy (PST) [2]. Over the last three decades, the management of patients with BC has been characterized by a steady trend toward less invasive axillary surgery. Two main strategies have contributed to this trend: the development of the sentinel lymph node biopsy (SLNB) procedure [3,4,5] and the introduction of primary systemic therapy (PST), including neoadjuvant chemotherapy, anti-HER2 therapies, and hormonal or biological treatments, indicated according to each tumor immunophenotype [6].

The high negative predictive value of sentinel lymph node biopsy (SLNB), exceeding 90%, implies that patients with negative SLNB (pN0) are unlikely to have additional affected lymph nodes. In fact, these patients can avoid axillary lymph

node dissection (ALND), with the consequent benefit of reduced morbidity and improved quality of life. Randomized clinical trials have demonstrated that SLNB is indeed equivalent to ALND in terms of locoregional disease control and survival in patients with early breast cancer [7,8,9, 10, 11]. The IBCSG 23-01 trial reported that performing ALND represents overtreatment in patients with early-stage CM whose GC has only isolated tumor cells (ITC) or mi (foci >0.2 mm - ⩽2 mm, pN1mi) and has no benefit in terms of disease-free survival (DFS) or overall survival (OS), these same results could be extrapolated to patients with ITC/mi after PST [12].

PST is currently used in patients with locally advanced breast cancer to convert inoperable tumors into resectable ones or to reduce tumors to a size compatible with breast-conserving surgery. It is also used to assess tumor response in vivo and, more recently, to achieve axillary lymph node biopsy (ALND) to avoid non-invasive lymph node biopsy [13,14]. N+ patients benefit most from PST by evaluating the response in both the breast and axilla, especially in TN and HER2-positive tumors [15]. Obtaining a positive PCR test after PST is strongly correlated with a more favorable prognosis in both disease-free survival (DFS) and overall survival (OS) [16]. Because PST can induce axillary fibrosis and alter lymphatic drainage, the main problems associated with sentinel lymph node biopsy (SLNB) are the low SCL identification rate and the high false-negative (FN) rate. Starting in 2005, the NSABP-27 trial initiated sentinel lymph node biopsy (SLNB) following neoadjuvant chemotherapy (NEO-CT), but it already indicated the use of two detection techniques, blue and 99mTc, to achieve a false negative rate (FN) below 10% [17]. In 2013, the results of the SENTINA trial delayed the possibility of safely performing SLN after NEO-CT due to high FN rates and a low SLN identification rate, both before and after NEO-CT [18]. Also in 2013, Boughey J, from MD Anderson, demonstrated the ability to reduce the false negative rate by extracting at least two sentinel lymph nodes [19]. In 2015, the Dutch study (MARI) performed initial positive lymph node labeling with a 125I seed, lowering the FN rate to 7% [20]. In 2016, Caudle A et al., at MD Anderson, coined the term TAD Target Axillary Dissection, combining the clip technique + SLNB, to identify positive lymph nodes in patients after receiving PST, thus reducing the FN rate to 2% [21]. Our technique is based on a modification of the latter, the main variant of which is the use of a nitinol® seed and not I125.

The objectives of our work were:

1. Assess the omission of ALND in patients with CM cT1-T3 cN1M0, with axillary response after PST.

2. Identify the axillary response in relation to molecular subtypes and verify if it has any utility in luminal patients.

2 Method

A descriptive and retrospective study is presented. The cohort consists of 100 patients, selected between January 2020 and March 2024 (99 females and 1 female), with breast cancer, cT1-T3N1M0, who received PST. 72 received chemotherapy and/or anti-HER2 therapy, and 28 patients received hormone therapy. 95 patients had invasive ductal carcinoma (IDC) and 5 had invasive lobular carcinoma (ILC). Mean tumor size was 35 mm (range 6-90 mm). Mean age was 53.5 years (range 28-81) (Table 1).

Table 1. Description of the study variables (n = 100)

Diagnosis (AP)	**n%**
IDC	95 (95)
ILC	5 (5)
Immunohistochemistry	
Luminal A	24 (24)
Luminal B	39 (39)
HER2	24 (24)
Triple Negative	13 (13)
Tumor Size at Diagnosis:	
T1	31 (31)

Diagnosis (AP)	n%
T2	58 (58)
T3	11 (11)
Histological Grade	
Grade 1	22 (22)
Grade 2	58 (58)
Grade 3	20 (20)
Surgery	
Breast-Conserving Surgery	81 (81)
Mastectomy	19 (19)

AP: anatomical pathology; n: sample size; IDC: Invasive Ductal Carcinoma; ILC: (Invasive Lobular Carcinoma)

All biopsies underwent immunohistochemistry. The CM subtypes and their respective treatments were:

• Luminal A, 24 patients:

6 received neoadjuvant chemotherapy AC x 4 + Taxol x 12 cycles.

18 patients with NEO HT, premenopausal patients,

7 were blocked with goserelin + Letrozole x 6 months.

11 postmenopausal patients received Letrozole/Anastrazole x 6 months.

• Luminal B, 39 patients:

20 received neoadjuvant chemotherapy AC x 4 + Taxol x 12.

13 patients with NEO HT were treated with letrozole + ribociclib x 6 months. (Ribolaris trial).

4 patients received letrozole x 6 months.

2 patients received goserelin + letrozole.

HER2-positive, 24 patients: treated with trastuzumab + pertuzumab + taxol + or - AC x 4.

TN, 13 patients: treated with AC x 4 + Taxol x 12 + or -carboplatin.

A core needle biopsy (CNB) is always performed on the suspicious lymph node (FNA is NOT performed). Initially, up to two lymph nodes were marked, but now only one lymph node is marked. The most caudal of a maximum of three suspicious lymph nodes (cortical thickness > 3 mm) is marked with a metallic nitinol® (titanium + nickel) clip, preferably in a "U" shape, as this shape is easier for pathologists to locate during extemporaneous biopsy. The clip is usually placed at the time of the biopsy. All patients underwent mammography, ultrasound, and MRI before and after PST. Only patients with complete or greater than partial radiological response were included.

3 Circuit and technique

The day before surgery, between 10 and 11 a.m., external lymphography is performed in nuclear medicine to detect the SLN marked with a radioactive isotope. Approximately 4 mCi of 99mTc is injected subareolarly, and after 30-40 minutes, images are acquired to check the location of the sentinel lymph node(s). Then, on the day of surgery, at 8 a.m., before entering the hospitalization area, the patient goes to the breast radiology unit, where, under local anesthesia, a harpoon is placed in the node and, if necessary, also in the breast. They are then admitted to the hospital and, in the operating room, 2 cm^3 of subareolar methylene blue is injected 20 minutes before the start of surgery. One of the surgeons massages the breast for 5-10 minutes to facilitate the migration of the blue dye to the armpit (Figures 1 and 2). An X-ray of the removed lymph node(s) is performed to confirm the presence of the clip (Figure 3). The nodes, both the marked ones and the sentinel nodes, are then taken to the pathology laboratory. At our center, they are processed intraoperatively using the OSNA (one-step acid nucleic amplification) technique to determine the number of copies of cytokeratin 19 mRNA (CK 19) in the SLN. The process takes approximately 20 minutes. If the result is 0 to 250 mRNA copies, these are isolated

tumor cells; 250 to 5,000 copies are micrometastases; and more than 5,000 are macrometastases. Given the low probability of finding other affected nodes with OSNA < 25,000 [24], we have raised our cutoff for VAX. Therefore, in our series, where all nodes are evaluated by OSNA, except for clinical trials that do not include it, the sum of the copies reported in the nodes studied should not exceed 25,000 copies in order to avoid performing ALND.

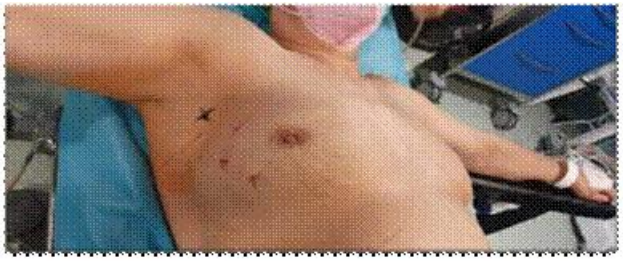

Figure 1. Conservative surgery with double marking in breast and marking in armpit.

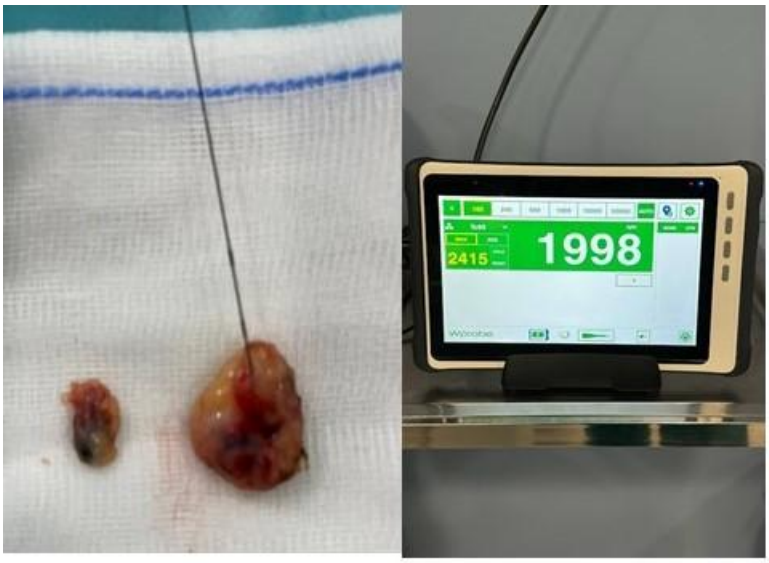

Figure 2. TAD. Ganglion with harpoon, methylene blue and hot (99mTc).

The wounds are closed with continuous absorbable sutures. Drains are not placed in the axilla or breast, except if a mastectomy and/or axillary lymph node dissection is performed. The patient is usually discharged first thing the following morning. Final biopsy results are available in an average of 7 days.

Adjuvant therapies, systemic treatment, and radiotherapy were discussed in the multidisciplinary tumor board. Treatments were planned according to standard clinical practice.

Inclusion criteria

- Patients with cT1-T3 N1 CM at diagnosis.
- Be over 18 years of age.
- Patients with N1 CM who have received primary systemic treatment, either hormone therapy, anti-HER2 treatment, or chemotherapy.
- Pre-PST positive lymph node marking.
- Patients who have undergone IVO surgery with informed consent.
- Patients with complete or greater than partial radiological response.

Exclusion criteria

• Patients with cN2 MC at diagnosis.

• Patients without clinical-radiological response to PST.

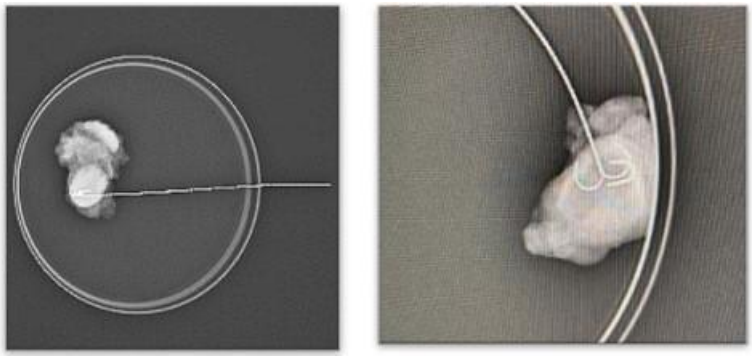

Figure 3. X-ray of lymph node: axillary lymphadenopathy with clip and harpoon

4 Results

100 patients with breast cancer received PST, achieving an axillary response in 52/100 cases (52%), with 34/52 (65%) achieving a complete pathological response (CPR) and 18/52 (34.6%) of these being 14 ypN1mi(sn) and 4 ITC ypN0 (i+) sn. Macrometastases were observed in 48 patients. ALND was performed in 33 patients and axillary RT in 15, most of which were included in the ADARNAT trial (Table 2). During 50 months of follow-up (mean 20 months, range 3-50), there were no axillary or distant relapses. In 14/33 (42%) lymphadenectomies, more metastatic nodes were found. Eighty-one conservative surgeries and 19 mastectomies were performed (Table 1).

Analyzing by molecular subtypes, the axillary pathological response occurred in:

• Luminal A: 6/24 (26%): 4ypN0 and 2ypmi(sn).

• Luminal B: 15/39 (42%): 8ypN0, 5 ypN1mi(sn), and 2 ITCypN0(i+) sn.

• HER2-positive: 21/24 (87%): 16ypN0, 4ypN1mi(sn), and 1 ITCypN0(i+) sn.

• Triple Negative: 10/13 (77%): 6ypN0, 3 ypN1mi(sn), and 1 ITCypN0(i+) sn.

Table 2. Descriptive analysis of directed axillary dissection. (n=100)

TAD	n%
N° SLN	
1	5 (5)
2	23 (23)
3	42 (42)
4	22 (22)
5 or more	8 (8)
PR (Pathological Response) result of the lymph node	
Pathological axillary response	52 (52)
Complete	34
ITC isolated tumor cells	4
Micrometastases	14
Macrometastases	48 (48)
No° of ALND	33
PR result in patients with ALND	
Only SLN positive	19 (57)
More tumor burden besides SLN	14 (42)
Coincidence of SLN with seed marking	88 (8)

It is worth noting that 45% of the ypN1mi(sn) lymph nodes analyzed by the OSNA technique had a low tumor burden, between 250 and 500 mRNA copies. 80% of patients had histological grade 2 or 3 (Table 2).

There were no serious complications during hookwire placement, nor any significant bleeding to report.

No migration of the lymph node clip was observed, despite this being one of our initial concerns. A 99% detection rate of the clipped axillary lymph node was achieved; only in one patient was the hookwire not successfully placed in the marked node. The mean number of lymph nodes in the TAD was 3.05 (Range 1-7). The concordance rate between the sentinel lymph node and the marked lymph node was 88% (88/100) (Table 2).

Among the patients who underwent ALND, in 20 of 33 cases (60.6%), no other metastatic lymph nodes were found; in the remaining 13, 5 had only 1 positive lymph node, and 6 patients had between 2 and 4 lymph nodes. It is noteworthy that 2 patients with complete radiological response and invasive lobular carcinoma had 10 and 17 additional lymph nodes, respectively, on ALND.

5 Discussion

The TAD, validated in the literature [19,20,21], minimizes the possibility of FN. In our case, we make a modification in the use of the seed, using a nitinol clip in the shape of a "u" preferably and not a 125I seed. In this way, we do not have the difficulty of handling a radioactive seed; our radiologists have had practically no problems in the location of the seed, especially when there is a complete radiological response.

At the IVO, the technique is feasible thanks to the collaborative work of the surgery, medical oncology, radiation oncology, radiology, nuclear medicine, and pathology departments. More than 50% of the cohort had a lymph node response, either complete or as an ITC or MI, thus avoiding axillary lymph node dissection and its associated morbidity.

Moo et al. argued that axillary lymphadenectomy should be omitted only in cases where the axillary pCR lymph node is completely negative, but not when ITC or micrometastases remain due to the high risk of other positive lymph nodes [22]. However, this study could be criticized because the axilla was almost always evaluated clinically only, positive lymph nodes were not labeled, and the tracer was used at the discretion of the surgical team.

It seems obvious that patients with residual axillary disease after Primary Systemic Therapy (PST) would have a worse prognosis compared to patients who achieve a pathological complete response (pCR). However, it is not entirely clear whether a low residual tumor burden influences prognosis in the same way. In particular, the clinical importance of axillary micrometastasis following PST has not yet been determined.

Analyzing the pathological status of lymph nodes after Primary Systemic Therapy (PST) in a pilot cohort of patients diagnosed cN+, converted to ypN-, Tinterri et al., in Milan, had preliminary evidence that patients with SLN micrometastatic ypN1mi(sn) have OS and DFS similar to those of pCR, ypN0(sn) patients. Conversely, these results were significantly worse in ypN1/3(sn) patients [23]. These findings are in line with the recent Dutch study by Van Nijnatten et al., who evaluated prognosis according to axillary residual disease in N+ patients and showed that patients with ypN0 and ypN1mi have similar long-term DFS and OS, while patients with ypN1-3 have a significantly less favorable prognosis [25]. It is also possible that in the vast majority of patients with micrometastases after PST, ALND is unnecessary, as demonstrated by the IBCSG 23-01 study in initial cN0 surgery. As in the NEONOD 2 study [23], we intend to verify whether it is oncologically safe not to perform axillary lymphadenectomy in those patients with axillary response, either complete or with little residual burden.

These clinical trials [12,23,24,25], in conjunction with the experience of MD Anderson (21), are what led us to propose this new surgical approach for managing the axilla after primary systemic therapy (PST), with very good results both in lymph node detection and, so far, in local recurrence, overall survival (OS), and disease-free survival (DFS).

Comparing our results with three large series in the literature [26,27,28], we see that the local recurrence rates are very low, even in those studies that did not use marking clips on the affected lymph nodes, not exceeding 2%. In fact, in the IEO study, published in 2023 with 222 cN1 cases and a negative conversion rate of 55%, similar to ours, the local

recurrence rate does not exceed 1.6% [26].

In response to the primary objective, we have been able to omit axillary lymphadenectomy in 51% of N1 breast cancer patients with axillary pathological response (RPA) after primary systemic therapy (PST). Our lymph node detection rate is 99%, and our mean number of extracted lymph nodes (3.05) leads us, once again, to affirm the performance of targeted axillary dissection (TAD) after neoadjuvant chemotherapy (NAC), as described in the literature [26,28].

Regarding the question of the most responsive subtypes, HER2-positive and triple-negative (TN) are by far the ones that achieve the highest rates of axillary conversion to negative. In our case, the rates were 86% and 66% respectively, which is consistent with the work of Barrio et al. [27], which included only TN and HER2-positive patients and reported axillary response rates of 90%, with only a single patient experiencing regional recurrence at three years. Therefore, we believe that these molecular subtypes are the ones for which we can truly avoid ALND. The problem, as always, lies with Luminal B tumors, which have a response rate of about 40% and often remain somewhat in a gray area, requiring case-by-case analysis; when they do not respond, ALND should be performed. In the case of Luminal A tumors, with such a low response rate of 25%, we believe that if the axilla has one or two positive nodes at diagnosis, it makes little sense to wait for its conversion to negative. Instead, the decision should be based on the response of the tumor in the breast, and axillary treatment should be considered according to the Giuliano criteria.

Responding to the primary objective, we have been able to omit axillary lymphadenectomy in 51% of N1 breast cancer patients with RPA after PST. Our lymph node detection rate is 99%, and our mean number of extracted lymph nodes (3.05) leads us, once again, to affirm the performance of TAD after QT, as described in the literature [26,28].

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Regarding not performing ALND in cases of isolated tumor cells or micrometastases, perhaps the most critical point: the probability of finding additional nodes in this scenario does not exceed 10%, as we see in the series by Moral P et al., [28]. Therefore, these patients, who will also receive radiotherapy, would not have a higher risk of regional recurrence. In our experience, in the case of Macrometastasis, we have found 40% of additional nodes, but so far we have not had any axillary or distant recurrences.

Definitely, as we see in a 2020 review by Piltin et al., there has been a gradual increase since 2009 in the use of SLNB in patients with N+ disease after PST, leading to a reduction of ALND by more than 50% during the period 2015-2019 [29].

While some major hospitals do not mark the positive node at the outset and perform only SLNB, the main scientific societies (NCCN, SESPM, St. Gallen Consensus) recommend, as in our practice, targeted axillary dissection, extracting the previously marked node and also performing the sentinel node technique with dual tracers; thus obtaining at least 3 lymph nodes [30]. In conclusion, 52% of the cohort had an axillary response, thus avoiding ALND. The HER2-positive and TN subtypes definitively have the highest response rates, between 60% and 80%. The benefit in Luminal A is minimal; the

intention to negate the axilla is controversial. TAD is an oncologically safe procedure; not inferior to ALND.

Ethical Responsibilities: All patients have signed the informed consent form. The information of the patients included in our work has been treated anonymously and confidentially. The database generated by our unit is only accessible by members of the team and is protected from unauthorized use by persons outside the research. This work was presented, approved, and is followed by the Multidisciplinary Tumor Committee of the Valencian Institute of Oncology (IVO). The treatment, communication, and transfer of personal data of all participants comply with the provisions of the *Organic Law on Data Protection and Guarantee of Digital Rights* and follow the bioethics norms of the *Declaration of Helsinki of the World Medical Association* on ethical principles for medical research. Funding: This research has not received any funding from agencies of the public sector, commercial sector, or non-profit entities. It is declared that the study was conducted with the same materials, personnel, and resources of the IVO. Acknowledgments: To all our patients, who are warriors in the fight against this disease, and to all the medical-scientific and administrative personnel of the IVO who allow us to fulfill our work with professionalism, speed, and ethics.

Conflicts of interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.

[2] Sociedad Española de Oncología Médica. SEOM. Las cifras de cáncer de España. (consultado 09 de agosto 2023), Disponible en: URL: www.seom.org.

[3] Giuliano A, Kirgan D, Guenther M, Morton D. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg. 1994; 220(3):391-401.

[4] Giuliano A. The evolution of sentinel node biopsy for breast cancer: Personal experience. Breast J. 2020;26(1):17-21.

[5] Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg V, Shriver C, et al. The sentinel node in breast cancer - a multicenter validation study. N EnglJ Med. 1998;339:941-946.

[6] Fisher B, Brown B, Mamounas E, Wieand S, Robidoux A, Margolese RG, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol. 1997;15: 2483-2493.

[7] Mansel RE, Fallowfield L, Kissin A, Goyal RG, Newcombe J, Dixon M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANACH trial. J Natl Cancer Inst. 2006;98:599-609.

[8] Ashikaga T, Krag DN, Land SR, Julian TB, Anderson SJ, Brown AM, et al. Morbidity results of the NASBP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. J Surg Oncol. 2010;102:111-118.

[9] Veronesi U, Paganelli G, Viale A, Luini S, Zurrida V. Galimberti V, et al. A randomized comparison of sentinel node biopsy with routine axillary dissection in breast cancer. N EnglJ Med. 2003;349:546-553.

[10] Giuliano A, Ballman K, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of axillary dissection vs. no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis. The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA. 2017;318(10):918-926.

[11] García-Etienne C, Mansel R, Tomatis M, Heil J, Bingazoil L, Ferrari A, et al. Trends in axillary node dissection

for early-stage breast cancer in Europe: Impact of evidence on practice. Breast. 2019;45:89-96.

[12] Galimberti V, Cole BF, Viale G, Veronesi P, Vicini E, Intra M, et al. International Breast Cancer Study Group Trial 23-01. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol. 2018;19(10):1385-1393.

[13] Budzar AU, Valero V, Ibrahim NK, Francis D, Broglio KR, RTheriault RL, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: An update of the initial randomized study population and data of additional patients treated with the same regimen. Clin. Cancer Res. 2007;13:228-233.

[14] Mamtani AV, Barrio TA, King KJ, VanZee G, Plitas M, Pilewskie, et al. How often does neoadjuvant chemotherapy avoid axillary dissection in patients with histologically confirmed nodal metastasis ? Results ofa prospective study. Ann Surg Oncol. 2016;23:3467-3474.

[15] Hennessy BT, Hortobagyi GN, Rouzier R, Kuerer H, N. Sneige A,Budzar U, et al.Outcome after pathological complete eradication of cytologically proven breast cancer node metastases following primary chemotherapy. J Clin Oncol. 2005;23:9304-9311.

[16] Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet. 2014;384:164-172.

[17] Mamounas EP, Brown A, Anderson S, Smith R, Julian T, Miller B, Bear HD, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: Results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2005;23(12):2694-702.

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

[19] 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;310:1455-1461.

[20] Donker M, Straver ME, Wesseling J, Loo CE, Schot M, Drukker CA, et al. Making 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):378-382.

[21] 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 elective Evaluation of clipped nodes: Implementation of targeted axillary dissection. J Clin Oncol. 2016;34(10):1072-1078.

[22] Moo TA, Edelweiss M, Hajiyeva S, Stempel M, Raiss M, Zabor EC, et al. Is low-volume gisease in the sentinel node after neoadjuvant chemotherapy an indication for axillary dissection? Ann Surg Oncol. 2018;25(6):1488-1494.

[23] Tinterri C, Canavese G, Bruzzi P, Dozin B. NEONOD 2: Rationale and design of a multicenter non- inferiority trial to assess the effect of axillary surgery omission on the outcome of breast cancer patients presenting only micrometastasis in the sentinel lymph node after neoadjuvant chemotherapy. Contemp Clin Trials Commun. 2019;23;17:100496.

[24] Peg V, Sansano I, Vieites B, Bernet L, Cano R, Córdoba A, et al. Role of total tumour load of sentinel lymph node on survival in early breast cancer patients. Breast. 2017;33:8-13.

[25] Van Nijnatten TJ, SimonsJM, MoossdorffM, de Munck L, Lobbes MB, van der Pol CC, et al. Prognosis of residual axillary disease after neoadjuvant chemotherapy in clinically node-posiIve breast cancer patients: Isolated tumor cells and micrometastases carry a beter prognosis than macrometastases. Breast Cancer Res Treat. 2017;163(1):159-166.

[26] Galimberti V, Ribeiro Fontana SK, Vicini E, Morigi C, Sargenti M, et al. "This house believes that: Sentinel node biopsy alone is better than TAD after NACT for cN+ patients". Breast. 2023;67:21-25.

[27] Barrio AV, Montagna G, Mamtani A, Sevilimedu V, Edelweiss M, Capko D, 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):1851-1855.

[28] Moral P, Delgado S, Ballester H, Ponce J, Martin T, Peiró G. Biopsia del ganglio centinela y disección axilar dirigida en mujeres con cáncer de mama y axila positiva en el momento del diagnóstico: caminando hacia el futuro. Revista de Senología y Patología Mamaria. 2023;(36): 100402.

[29] Piltin MA, Hoskin TL, Day CN, Davis J Jr, Boughey JC. Oncologic outcomes of sentinel lymph node surgery after neoadjuvant chemotherapy for node-positive breast cancer. Ann Surg Oncol. 2020 ;27(12):4795-4801.

[30] Vento G, Fuster C, Maisto V, Rios A, Gavilá J, Guerrero A, et al. Disección axilar dirigida tras tratamiento sistémico primario en cáncer de mama N1. Validación de la técnica y experiencia a los 4 años. Rev Senol Patol Mamar. 2024;37(3):100605.