Original Article

Sentinel Lymph-Node Biopsy or Targeted Axillary Dissection in Node-Positive Breast Cancer Patients Submitted to Neoadjuvant Therapy?

Biópsia do Gânglio Linfático Sentinela ou Dissecção Axilar Orientada em Doentes com Cancro da Mama com Gânglios Positivos Submetidas a Terapêutica Neoadjuvante?

Nuno Sousa[1*], Catarina Pinto[2], Bárbara Peleteiro[1,3,4,5], José Fougo[1,6]

1. Breast Center, ULS de São João, Porto, Portugal
2. ENT department, ULS de Gaia e Espinho, Porto, Portugal
3. EPI Unit, Institute of Public Health, University of Porto, Porto, Portugal
4. Laboratory for Integrative and Translational Research in Population Health, University of Porto, Porto, Portugal
5. Department of Public Health and Forensic Sciences, and Medical Education, Faculty of Medicine, University of Porto, Porto, Portugal
6. Department of Surgery and Physiology, Faculty of Medicine, University of Porto, Porto, Portugal

Corresponding Author/Autor Correspondente:
Nuno Sousa [nunomgbsousa@gmail.com]
Breast Center, ULS de São João, Alameda Prof. Hernâni Monteiro, 4200-319 Porto

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ABSTRACT

Introduction: Targeted axillary dissection (TAD) was designed for nodal staging in cN+ breast cancer (BC) patients submitted to neoadjuvant therapy (NAT). A recent study questioned the need to mark suspicious nodes pre-NAT.

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Methods: cT1-4 N1-2 BC patients scheduled for NAT were selected for retrospective appraisal. Patients were divided according with SLNB/TAD and ycN0/ycN+ status. Detection rate (DR), concordance rate (CR), predictive factors of successful clipped-node biopsy (CNB), sentinel node (SN) pathological complete response (pCR) and of additional non-sentinel lymph node (NSLN) involvement were assessed. Oncological outcomes were evaluated.
Results: The study included 85 consecutive patients. DR was 83.6%, 98.8% and 98.8% for CNB, SLNB and TAD, respectively. CNB did not drive management changes as every CN was sentinel (CR 100.0%). CNB was unsuccessful in 10 patients with 2 (20.0%) re-operated with no additional benefit. Removal of at least 3 SN was associated with successful CNB (p=0.001). Fewer (1 *vs* 2) suspicious nodes at diagnostic echography and triple-negative or HER2 biological subtype were predictive of SN pCR. Lymph-vascular invasion was predictive of additional NSLN involvement in pSN+ patients (p=0.008). Disease-free survival was worse in ypSN+ (p=0.029) and the only regional recurrence was in an axillary lymph node dissection (ALND) patient. There was no difference in the overall survival between ALND and no-ALND patients (p=0.270).
Conclusion: CNB is superfluous if 3 or more SN are retrieved using a dual mapping technique. It is safe to omit ALND if pCR of the SN is achieved. Future studies should assess the need for ALND in ypSN+ patients.

Keywords: Breast Neoplasms; Lymph Node Excision; Lymph Nodes/surgery; Lymphatic Metastasis; Neoadjuvant Therapy; Sentinel Lymph Node/surgery; Sentinel Lymph Node Biopsy.

RESUMO

Introdução: A disseção axilar orientada (DAO) foi desenvolvida para o estadiamento ganglionar de doentes com cancro de mama com gânglios positivos ao diagnóstico submetidas a terapia neoadjuvante (TNA). Um estudo recente questionou a necessidade de marcar os gânglios suspeitos pré-TNA.
Métodos: Doentes com cancro de mama cT1-4 cN1-2 orientadas para TNA foram selecionadas para análise retrospetiva. As doentes foram divididas de acordo com o tipo de cirurgia axilar (biópsia de gânglio sentinela, BGS, *versus* DAO) e estado pós-TNA (ycN0 *versus* ycN+). A taxa de deteção (TD), concordância, fatores preditivos de biópsia de gânglio clipado, BGC, com sucesso, fatores preditivos de resposta patológica completa nos gânglios sentinela, GS, e fatores preditivos de metástases adicionais em gânglios não sentinela, GNS, foram pesquisados. Também avaliamos os ***outcomes*** oncológicos.
Resultados: O estudo incluiu 85 doentes consecutivas. A TD foi de 83,6%, 98,8% e 98,8% para BGC, BGS e DAO, respectivamente. A BGC não motivou alterações no tratamento, uma vez que todos os gânglios clipados eram GS (concordância 100,0%). A BGC não foi bem sucedida em 10 doentes sendo que 2 (20,0%) foram re-operadas sem benefício adicional. A remoção de pelo menos 3 GS foi associada a BGC bem sucedida (p=0,001). Menos (1 *vs* 2) gânglios suspeitos à ecografia diagnóstica e tipo biológico triplo negativo ou enriquecido em HER2 foram preditivos de resposta patológica completa nos GS. A presença de invasão linfovascular foi preditiva de envolvimento adicional de GNS (p=0,008). A sobrevida livre de doença foi menor em doentes ypGS+ (p=0,029) e a única recorrência regional foi numa doente que realizou esvaziamento ganglionar axilar. Não houve diferença na sobrevida geral entre doentes submetidas *versus* doentes não submetidas a esvaziamento ganglionar axilar (p=0,270).
Conclusão: A BGC é supérflua se pelo menos 3 GS forem obtidos utilizando uma técnica de mapeamento dupla.
É seguro omitir o esvaziamento ganglionar axilar se for obtida uma resposta patológica completa nos GS. Estudos futuros devem avaliar a necessidade de esvaziamento ganglionar axilar em doentes ypGS+.

Palavras-chave: Biópsia do Gânglio Linfático Sentinela; Excisão do Gânglio Linfático; Gânglio Linfático Sentinela/cirurgia; Gânglios Linfáticos/cirurgia; Metástases Linfáticas; Neoplasias da Mama; Tratamento Neoadjuvante.

INTRODUCTION

In the setting of breast cancer (BC) management, neoadjuvant therapy (NAT) allows downstaging of the primary tumor and of lymph node (LN) metastasis, de-escalating surgical treatment in some patients.[1,2] Correct nodal staging after NAT is important to select patients who can be spared the morbidity of an axillary lymph node dissection (ALND).[3,4]

In initially cN+ patients submitted to NAT, uneven tumor regression and fibrosis in the LN leads to disruption of the reticule-endothelial system.[5,6] This can account for the historically lower detection rate (DR) and higher false negative rate (FNR) of sentinel lymph node biopsy (SLNB) after NAT,[7,8] because the radio-isotope (RI) used for the sentinel node (SN) mapping depends on active uptake by the reticuloendothelial cells.[9] Performance of a dual mapping technique using patent

blue dye (PBV) and RI allowed a DR of 87.8% in the SENTINA trial[10] and a FNR of 10.8% in the ACOSOG Z1071 trial.[11] These values were short of the desired 90% cut-off for DR and 10% for FNR.[12] Studies such as the GANEA 2[13] and SN FNAC[14] further proposed the removal of at least 2 sentinel lymph nodes and the use of immunohistochemistry, respectively.

Clinicians have addressed this issue by marking the clinically positive nodes before NAT using different procedures, such as using radio-iodine seeds,[15] ferromagnetic seeds,[16] ink,[17] carbon tattoo[18] or an ultrasound-visible clip.[19] Clipped node biopsy (CNB) involves marking one or two of the most suspicious nodes at presentation with an ecographically visible titanium clip. After NAT, the patient undergoes targeted axillary dissection (TAD), in which CNB is performed along with SLNB.[20,21] Authors have consistently reported a FNR below 10% with this technique.[22]

One fluorescent dye – indocyanine green (ICG) – is of passive drainage, which means that it is not affected by changes in the nodes induced by NAT.[23,24] Our center uses subareolar PBV dye together with peritumoral ICG to identify the sentinel lymph node (SN)[25,26]; in a previous study, we evaluated the concordance rate (CR) between CNB and SLNB in cN1 patients that converted to ycN0 after NAT. We obtained a CR of 100% in a small series of 37 patients.[27] After this publication, the marking of the biopsied lymph node (LN) was done only at clinician and/or radiologist criteria.

We hypothesized that it might be safe to rely on SLNB after NAT to guide further axillary treatment, eliminating the need to mark the involved nodes. We assessed the DR of CNB *versus* SLNB *versus* TAD in ycN0 and ycN+ patients. Additionally, we evaluated the CR in TAD patients. Factors associated with successful CNB, predictive factors of pathological complete response (pCR) of the SN and predictive factors of additional non-sentinel lymph node (NSLN) involvement in ypN+ sn patients were searched. Furthermore, the outcomes associated with each axillary procedure were compared.

METHODS

1. STUDY TYPE AND POPULATION

This retrospective, unicentric study included consecutive patients treated between 1st July 2019 and 31st December 2023 at the Breast Center of ULS São João, Porto, Portugal (Fig. 1). Patients with cT1-4c cN1-2 cM0 BC who performed NAT were eligible. All patients were biopsy-proven cN+. Patients who had previous ipsilateral breast and/or axillary surgery were excluded.

The study was approved by the conjoint Ethics Committee of ULS São João and Faculty of Medicine of Porto University – project number 83/24.

2. PATIENT GROUPS

One of the objectives was to evaluate the DR of SLNB using passive vital dyes. After NAT, patients either converted to

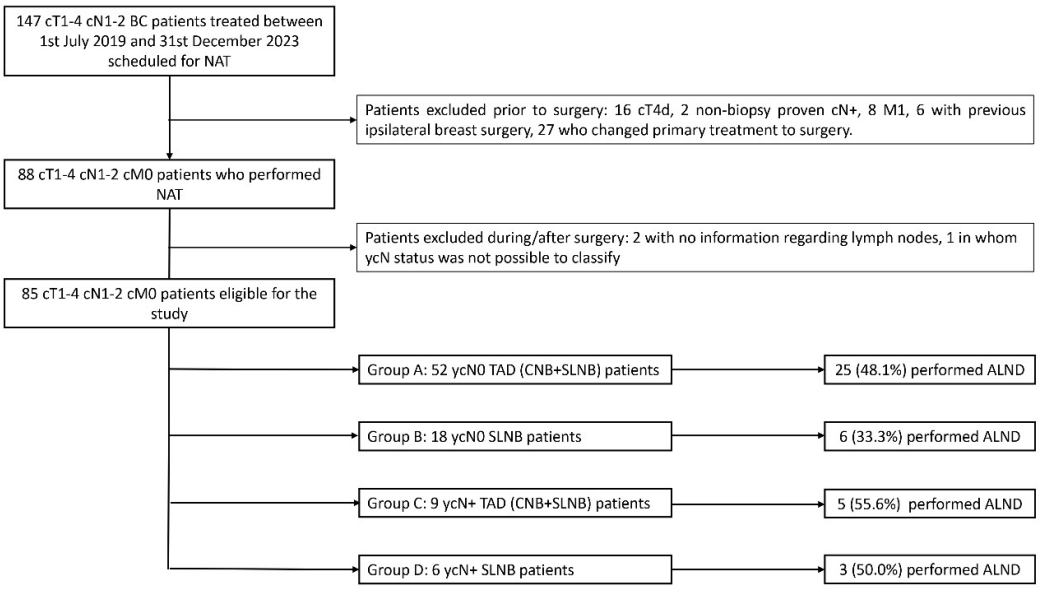

Figure 1. Patients included in the study.

ALND - axillary lymph-node dissection; BC - breast cancer; CNB - clipped-node biopsy; ICG - indocyanine green; PBV - patent blue V dye; SLNB - sentinel--lymph node biopsy; TAD - targeted axillary dissection

ycN0 or remained ycN+. The ycN status was assessed by physical exam and imaging (mammography, echography and breast magnetic resonance imaging) after NAT. Since ycN+ patients had suspected tumor burden in the nodes during clinical and/or imageology re-evaluation, the tumor bulk could have affected the passive flow of dyes during lymph node mapping.[9,28] Therefore, patients were not only divided according to the first axillary procedure, but also ycN status: ycN0 TAD (Group A), ycN0 SLNB (Group B), ycN+ TAD (Group C) and ycN+ SLNB (Group D).

3. AXILLARY PROCEDURES

SLNB was undertaken by a combined method[24,25] that merges the peritumoral injection of ICG (1 cc, 5 mg, Verdye, Diagnostic Green, Ireland) with the subareolar plexus injection of PBV dye (1 cc, 2.5%, Guerbet, France); fluorescence was identified with the peri-operative use of an infrared hand-held probe (Photo Dynamic Eye, Hamamatsu, Japan); every blue and/or fluorescent and/or suspicious LN was considered a SN and was excised.

TAD consisted of CNB plus SLNB. Before initiating NAT, patients had their one to two more suspicious nodes marked with an ecographically visible titanium clip (HydroMARK™) at the time of diagnostic echography. CNB was performed using axillary ultrasound immediately after anesthetic induction and PBV+ICG injection[19,20]; when the CN was identified in the ultrasound, the surgeon placed a pen-dye skin mark in the axilla, in the projection of the CN. The nodes retrieved were radiographed to confirm the presence of the clip. CNB was successful if at least 1 node housed a clip. The CN was considered a SN if it was blue and/or fluorescent and/or suspicious.

If TAD/SLNB was unsuccessful, or if the nodes obtained were positive (ITC–isolated tumor cells, micro- or macro-metastasis), the patient was submitted to Berg levels 1+2 ALND.[29,30] ALND was performed immediately after SLNB/TAD or as a second procedure.

4. PATHOLOGY WORKUP

Nodes retrieved during the first axillary procedure were analyzed by conventional hematoxylin-eosin pathology or one-step nucleic acid assay (OSNA).[30-32] In the case of complete ALND, the LN was analyzed by conventional pathology.

5. BREAST SURGERY AND ADJUVANT TREATMENTS

Breast-conserving surgery or total mastectomy as well as adjuvant treatments were performed according to the breast center protocols, the multidisciplinary tumor board meeting and after discussion with the patient. Adjuvant treatments consisted of chemotherapy, anti-HER2 agents, endocrine therapy, whole breast irradiation and regional node irradiation.[33]

6. DETECTION RATE (DR) AND CONCORDANCE RATE (CR)

All patients performed SLNB. Patients in groups A and C also performed CNB as part of the TAD procedure. In all groups, we assessed the sentinel node detection rate (SN-DR). This was the proportion of patients with at least 1 blue and/or fluorescent and/or suspicious node retrieved, regardless of the presence of a clip. Additionally, in groups A and C we assessed the clipped-node biopsy detection rate (CN-DR). This was, specifically, the proportion of patients with at least 1 CN retrieved, regardless of the presence of blue and/or fluorescent dye in those nodes. In both-groups, we also evaluated the targeted axillary dissection detection rate (TAD-DR), which was the proportion of patients with at least 1 SN and/or 1 non-dyed CN retrieved. The reference value for the DR was >90%.[14,34]

7. DATA ANALYSIS

A database containing patient, tumor and node characteristics was created and all statistical analyses were performed using IBM SPSS Statistics v27.0, Chicago, USA. Frequencies were used for qualitative variables and medians for quantitative variables. Pearson's chi-squared and Fisher's exact test were used for the comparison of proportions, as appropriate. Mann-Whitney U test and Kruskal-Wallis were performed for comparison of medians, as appropriate. Survival analyses were performed using the Kaplan–Meier method and the log-rank test was used to compare estimates for overall survival (OS) and disease-free survival (DFS) across groups.

RESULTS

1. GENERAL

A total of 85 patients were included (Table 1) and the majority were cT2N1G3 invasive ductal carcinoma. The predominant biological subtype was Luminal HER2 negative. NAT was chemotherapy for 80 (94.1%), endocrine therapy for four (4.7%) and both for one (1.2%) patient. Afterwards, 70 (82.4%) of cases converted to ycN0. There were 61 (71.8%) TAD (CNB+SLNB) procedures. There was no significant difference between groups in the number of SN excised (p=0.177) (Table 2). ALND was performed in 39 (45.9%) of patients and there was no difference in the number of NSLN excised (p=0.799) or the number of NSLN metastasized (p=0.253) between the 4 groups of patients. Overall NSLN

Table 1. Patient characteristics.

	All patients, n = 85	TAD (CNB+SLNB), n = 61	SLNB, n = 24	p†
Age in years, median (range)	49 (26-90)	45 (26-78)	55 (39-90)	0.001
Follow-up time in months, median (range)	30.0 (8-60)	32.0 (8-60)	18 (10-52)	0.005
Affected side, n (%)				
Left	46 (54.1)	34 (55.7)	12 (50.0)	0.633
Right	39 (45.9)	27 (44.3)	12 (50.0)	
Previous contralateral breast cancer, n (%)				
Yes	2 (2.4)	0 (0.0)	2 (8.3)	0.077
No	83 (97.6)	61 (100.0)	22 (91.7)	
BRCA1, n (%)				
Positive	1 (1.2)	0 (0.0)	1 (4.2)	0.136
Negative	56 (65.9)	43 (70.5)	13 (54.2)	
Not assessed	28 (32.9)	18 (29.5)	10 (41.7)	
BRCA2, n (%)				
Positive	2 (2.4)	1 (1.6)	1 (4.2)	0.304
Negative	55 (64.7)	42 (68.9)	13 (54.2)	
Not assessed	28 (32.9)	18 (29.5)	10 (41.7)	
cT, n (%)				
1	16 (18.8)	12 (19.7)	4 (16.7)	0.565
2	53 (62.4)	38 (62.3)	15 (62.5)	
3	15 (17.6)	11 (18.0)	4 (16.7)	
4	1 (1.2)	0 (0.0)	1 (4.2)	
cN, n (%)				
1	80 (94.1)	59 (96.7)	21 (87.5)	0.134
2	5 (5.9)	2 (3.3)	3 (12.5)	
Stage, n (%)				
II	64 (75.3)	49 (80.3)	15 (62.5)	0.086
III	21 (24.7)	12 (19.7)	9 (37.5)	
Histology at CB, n (%)				
Ductal	75 (88.2)	58 (95.1)	17 (70.8)	0.006
Lobular	5 (5.9)	1 (1.6)	4 (16.7)	
Other	5 (5.9)	2 (3.3)	3 (12.5)	
Grade at CB, n (%)				
II	16 (18.8)	12 (19.7)	4 (16.7)	0.750
III	69 (81.2)	49 (80.3)	20 (83.3)	
Biological subtype at CB, n (%)				
Luminal HER2-	43 (50.6)	30 (49.2)	13 (54.2)	0.075
Luminal HER2+	21 (24.7)	19 (31.1)	2 (8.3)	
HER2-enriched	8 (9.4)	4 (6.6)	4 (16.7)	
Triple negative	13 (15.3)	8 (13.1)	5 (20.8)	
Neoadjuvant therapy, n (%)				
Chemotherapy	80 (94.1)	59 (96.7)	21 (87.5)	0.134
Hormone therapy	4 (4.7)	2 (3.3)	2 (8.3)	
Both	1 (1.2)	0 (0.0)	1 (4.2)	
ycN, n (%)				
ycN0	70 (82.4)	52 (85.2)	18 (75.0)	0.344
ycN+	15 (17.6)	9 (14.8)	6 (25.0)	
Definitive breast surgery, n (%)				
Breast-conserving surgery	65 (76.5)	45 (73.8)	20 (83.3)	0.349
Total mastectomy	20 (23.5)	16 (26.2)	4 (16.7)	
ALND, n (%)				
Yes	39 (45.9)	30 (49.2)	9 (37.5)	0.331
No	46 (54.1)	31 (50.8)	15 (62.5)	
Final pathology, n (%)				
Benign	23 (27.1)	15 (24.6)	8 (33.3)	0.527
In situ	12 (14.1)	10 (16.4)	2 (8.3)	
Invasive	50 (58.8)	36 (59.0)	14 (58.3)	
Histology of invasive tumor, surgical specimen, n (%)				
Ductal NST	42 (49.4)	32 (52.5)	10 (41.7)	0.128
Lobular	4 (4.7)	1 (1.6)	3 (12.5)	
Mucinous	1 (1.2)	0 (0.0)	1 (4.2)	
Mixed NST/other	2 (2.4)	2 (3.3)	0 (0.0)	
Other	1 (1.2)	1 (1.6)	0 (0.0)	
Not applicable	35 (41.2)	25 (41.0)	10 (41.7)	
ypT, n (%)				
0	35 (41.2)	25 (41.0)	10 (41.7)	0.746
1	29 (34.1)	22 (36.1)	7 (29.2)	
2	19 (22.4)	13 (21.3)	6 (25.0)	
3	1 (1.2)	0 (0.0)	1 (4.2)	
4	1 (1.2)	1 (1.6)	0 (0.0)	

	All patients, n = 85	TAD (CNB+SLNB), n = 61	SLNB, n = 24	p†
ypN, n (%)				
0	43 (50.6)	30 (49.2)	12 (50.0)	
1	33 (38.8)	25 (41.0)	9 (37.5)	0.770
2	8 (9.4)	5 (8.2)	3 (12.5)	
3	1 (1.2)	1 (1.6)	0 (0.0)	
Perineural invasion, n (%)				
Yes	5 (5.9)	4 (6.6)	1 (4.2)	0.673
No	80 (94.1)	57 (93.4)	23 (95.8)	
Lymph-vascular invasion, n (%)				
Yes	17 (20.0)	13 (21.3)	4 (16.7)	0.768
No	68 (80.0)	48 (78.7)	20 (83.3)	
Multifocality, n (%)				
Yes	16 (18.8)	14 (23.0)	2 (8.3)	0.216
No	69 (81.2)	47 (77.0)	22 (91.7)	
Adjuvant chemotherapy, n (%)				
Yes	13 (15.3)	9 (14.8)	4 (16.7)	0.825
No	72 (84.7)	52 (85.2)	20 (83.3)	
Adjuvant breast irradiation, n (%)				
Yes	83 (97.6)	61 (100.0)	22 (91.7)	0.077
No	2 (2.4)	0 (0.0)	2 (8.3)	
Adjuvant axillary irradiation, n (%)				
Yes	84 (98.8)	61 (100.0)	23 (95.9)	0.019
No	1 (1.2)	0 (0.0)	1 (4.2)	
Adjuvant hormone therapy, n (%)				
Yes	64 (75.3)	49 (80.3)	15 (62.5)	0.086
No	21 (24.7)	12 (19.7)	9 (37.5)	
Adjuvant anti-HER2 therapy, n (%)				
Yes	29 (34.1)	23 (37.7)	6 (25.0)	0.266
No	56 (65.9)	38 (62.3)	18 (75.0)	
Vital status, n (%)				
Without cancer	77 (90.6)	55 (90.2)	22 (91.7)	0.819
With cancer	7 (8.2)	5 (8.2)	2 (8.3)	
Death by cancer	1 (1.2)	1 (1.6)	0 (0.0)	
First recurrence, n (%)				
None	78 (91.8)	55 (90.2)	23 (95.8)	
Local	2 (2.4)	2 (3.3)	0 (0.0)	0.273
Regional	1 (1.2)	0 (0.0)	1 (4.2)	
Distant	4 (4.7)	4 (6.6)	0 (0.0)	

† Mann-Whitney U, Pearson's chi-squared test/Fisher's exact test

Table 2. Evaluation of axillary status and procedures

	All, n = 85	Group A, n = 52	Group B, n = 18	Group C, n = 9	Group D, n = 6	p†
Specific DR, %						
SN	98.8	100.0		100.0		
CNB	83.3	82.7	94.4	88.9	100.0	-
TAD	98.8	100.0		100.0		
CR, %	100.0	100.0	-	100.0	-	
Number of SN excised, median (range)	3 (0-4)	3 (1-4)	3 (0-3)	2 (1-4)	3 (2-3)	0.177
Type of metastasis at the SN, n (%)						
Isolated tumor cells	2 (2.3)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	
Micrometastasis	8 (9.4)	7 (13.5)	0 (0.0)	1 (11.1)	0 (0.0)	
Macrometastasis	26 (30.6)	15 (28.8)	5 (27.8)	3 (33.3)	3 (50.0)	0.688
Metastasis*	2 (2.3)	1 (1.9)	0 (0.0)	1 (11.1)	0 (0.0)	
Non-metastasis	46 (54.1)	27 (51.9)	12 (66.7)	4 (44.4)	3 (50.0)	
Unsuccessful SN biopsy	1 (1.2)	0 (0.0)	1 (5.5)	0 (0.0)	0 (0.0)	
ALND, n (%)						
Yes	39 (45.9)	25 (48.1)	6 (33.3)	5 (55.5)	3 (50.0)	0.652
No	46 (54.1)	27 (51.9)	12 (66.6)	4 (44.5)	3 (50.0)	
Number of NSLN excised in ALND patients, median (range)		10 (2-16)	11 (3-14)	9 (3-13)	10 (10-14)	0.799
Number of NSLN with metastasis in ALND patients, median (range)	0 (0-12)	0 (0-12)	1 (0-6)	1 (0-3)	0 (0-1)	0.253
NSLN positivity rate, %	30.8	20.0	50.0	60.0	33.3	-

Group A consisted of ycN0 TAD patients; Group B were ycN0 SLNB patients; Group C consisted of ycN+ TAD patients; Group D were ycN+ SLNB patients; ALND-axillary lymph node dissection; CNB-clipped node biopsy; CR-concordance rate, DR-Detection rate; NSLN-non-sentinel lymph node; SN-sentinel node; SLNB-sentinel lymph node biopsy; TAD-targeted axillary dissection; *no discrimination of tumor size. † Kruskal-Wallis, Pearson's chi-squared test/ Fisher's exact test.

positivity rate was 30.8% and the highest NSLN positivity rate was observed in group C (60.0%). Time of follow-up was 32 months (range: 8-60) in the TAD patients *vs* 18 months (range: 10-52) in the SLNB patients (p=0.005).

2. GROUP A

This subsample consisted of 52 ycN0 TAD patients, with a median follow-up time of 32 months (range: 8-60). All patients had at least one SN retrieved (DR 100.0%) with 48 (92.4%) having two or more SN retrieved (Table 2). In 49 patients one clip was placed while three patients had two clips placed. In nine (17.3%) patients, no CN was recovered, but two or more SN were obtained (median: 3; range: 2-4). In the other 43 (82.7%) patients, every CN was sentinel; CR 100.0%. A total of 25 (48.1%) patients performed ALND, of which two (8.0%) had ITC, seven (28.0%) had micrometastasis, 15 (60.0%) had macrometastasis and one (4.0%) had positive SN but no discrimination of size of metastasis. Of these 25 patients, five (20.0%) had additional metastasized NSLN (4 had SN macrometastasis; one had unknow size of SN metastasis) and three (12.0%) had NSLN with indirect signs of metastasis (3 patients with macrometastasis).

3. GROUP B

This subsample consisted of 18 ycN0 SLNB patients, with a median follow-up time of 18 months (range: 10-52). SLNB was successful in 17 cases, with a median of 3 SLN excised (range: 1-3). DR 94.4% (Table 2). ALND was performed in six (33.3%) of patients because five (83.3%) had macrometastasis in the SLN and one (16.7%) had an unsuccessful SLNB. In the five patients with macrometastasis, three (60.0%) had NSLN with both indirect and direct signs of metastasis. The patient with unsuccessful SLNB did not have any involved nodes.

4. GROUP C

This subsample consisted of 9 ycN+ TAD patients, with a median follow-up time of 37 months (range: 21-52). All patients had at least one SN retrieved, with a DR of 100.0% (Table 2). Only one clip was placed per patient. In one (11.1%) patient, no CN was retrieved but three SN were excised. Of the remaining eight (88.9%) patients, six (75.0%) had two or more SN identified. CR was 100.0%. There were five (55.6%) ALND: one (20.0%) patient had micrometastasis in the SN and no additional NSLN involvement, three (60.0%) patients had macrometastasis in the SN and additional metastasized NSLN (of which one also had indirect signs of metastasis in the NSLN) and one (20.0%) patient had a positive sentinel node (metastasis size non-discriminated) and no additional involvement of the NSLN.

5. GROUP D

This subsample consisted of six ycN+ SLNB patients, with a median follow-up time of 16 months (range: 11-50). SLNB was successful in all cases with a median of three SLN excised (range: 3-6). DR 100.0% (Table 2). A total of three (50.0%) of patients underwent ALND, all of which had macrometastasis in the SLN. Of these, one (33.3%) had additional NSLN with both direct and indirect sign of metastasis

6. SUCCESS OF THE CNB PROCEDURE

Removal of three or more SN was the only factor associated with a successful CNB procedure (p=0.001). CNB was unsuccessful in 10 patients (9 group A, 1 group C). Of these 10 patients, one (10.0%) underwent TAD with two macrometastasized SN and no CN retrieved. After ALND, the CN was still not found. The possibility of leaving chemo-resistant disease in the axilla led to re-operation and the clip was found next to a node with a scar from a previous metastasis. In this case, the SN previously identified were the most informative ones and the patient experienced additional morbidity. In two (20.0%) patients the clip was found in a subcutaneous position in the pavement of the axilla, increasing operative time, searching for the clips. In four (40.0%) patients the clip was never found, despite additional imaging exams (no re-operation) – one was the group C patient. In one patient (10.0%), post-operative imaging exams revealed the clip and the patient was re-operated with the clip being inside of an axillary seroma. Also, two (20.0%) patients performed ALND due to metastasized SN and the clip was found in the product of ALND.

7. PREDICTIVE FACTORS OF NODAL INVOLVEMENT

For this analysis only patients with successful TAD/SLNB and complete information of important variables were considered (n=82), of which there were 46 (56.1%) patients with pCR in the SN and 36 (43.9%) patients with persistent nodal involvement (Table 3). A total of three patients were excluded from this analysis: one patient from group B because of unsuccessful SLNB and two patients (1 in group A and 1 in group C) whose SN was positive, but information about size of SN metastasis and information regarding other important variables were missing. Fewer suspicious nodes at initial axillary ultrasound (1 *vs* 2), aggressive biological subtypes (HER2 positive and triple negative tumors), breast-conserving surgery, pCR of the breast and absence of lymph-vascular invasion were factors significantly associated with SN pCR.

Of the 36 patients submitted to ALND because of SN positivity, 11 (30.6%) had metastasized NSLN. The presence

Table 3 – Factors associated with pathological complete response (pCR) in the sentinel nodes.

	ypN0sn (n=46)	ypN+sn (n=36#)	p†
Age at diagnosis, median (range)	49 (26-90)	46 (33-78)	0.397
Previous contralateral breast cancer, n (%)			0.501
Yes	2 (4.3)	0 (0.0)	
No	44 (95.7)	36 (100.0)	
Number of suspicious nodes at axillary ultrasound, median (range)	1 (1-4)	2 (1-5)	0.028
cT, n (%)			0.069
1	6 (13.0)	9 (25.0)	
2	34 (73.9)	18 (50.0)	
3	5 (10.9)	9 (25.0)	
4	1 (2.2)	0 (0.0)	
cN, n (%)			0.163
1	45 (97.8)	32 (88.9)	
2	1 (2.2)	4 (11.1)	
Stage at diagnosis, n(%)			0.095
II	38 (82.6)	24 (66.7)	
III	8 (17.4)	12 (33.3)	
Biological subtype, n (%)			0.005
Luminal HER2-	15 (32.6)	26 (72.2)	
Luminal HER2+	15 (32.6)	5 (13.9)	
HER2-enriched	6 (13.0)	2 (5.6)	
Triple negative	10 (21.7)	3 (8.3)	
Final surgery of the breast, n (%)			0.007
Breast-conserving surgery	40 (87.0)	22 (61.1)	
Total mastectomy	6 (13.0)	14 (38.9)	
Final pathology, n (%)			<0.001
No tumor identified	20 (43.5)	2 (5.6)	
In situ	7 (15.2)	5 (13.9)	
Invasive	19 (41.3)	29 (80.6)	
Histological type, n (%)			0.001
Ductal NST	17 (37.0)	23 (63.9)	
Lobular	1 (2.2)	3 (8.3)	
Mucinous	0 (0.0)	1 (2.8)	
Mixed NST + other	1 (2.2)	1 (2.8)	
Other	0 (0.0)	1 (2.8)	
Benign	27 (58.7)	7 (19.4)	
ypT, n (%)			<0.001
0	27 (58.7)	7 (19.5)	
1A	5 (10.9)	1 (2.8)	
1B	5 (10.9)	3 (8.3)	
1C	5 (10.9)	10 (27.8)	
2	2 (4.3)	15 (41.7)	
3	1 (2.2)	0 (0.0)	
4	1 (2.2)	0 (0.0)	
Perineural invasion, n (%)			0.163
Yes	1 (2.2)	4 (11.1)	
No	45 (97.8)	32 (88.9)	
Lymph-vascular invasion, n (%)			0.026
Yes	5 (10.9)	11 (30.6)	
No	41 (89.1)	25 (69.4)	
Multifocality, n (%)			0.584
Yes	8 (17.4)	8 (22.2)	
No	38 (82.6)	28 (77.8)	
Number of CN excised, median (range)	1 (0-2)	1 (0-2)	0.957
Number of SLN excised, median (range)	2 (1-4)	2 (1-4)	0.493

† patients who underwent ALND because of unsuccessful TAD/SLNB were excluded from the analysis; † Mann-Whitney U, Pearson's chi-squared test/Fisher's exact test.

Table 4 – Factors associated with additional positive NSLN in pSN+ patients (n=36).

	NSLN- (n=25)	NSLN+ (n=11)	*p*†
Age at diagnosis in years, median (range)	44 (33-73)	51 (38-78)	0.149
Previous contralateral breast cancer, n (%)			-
Yes	0 (0.0)	0 (0.0)	
No	25 (100.0)	11 (100.0)	
Number of suspicious nodes at ecography, median (range)	1 (1-4)	2 (1-5)	0.359
cT, n (%)			0.926
1	6 (24.0)	3 (27.3)	
2	13 (52.0)	5 (45.5)	
3	6 (24.0)	3 (27.3)	
4	0 (0.0)	0 (0.0)	
cN, n (%)			0.944
1	22 (88.0)	10 (90.9)	
2	3 (12.0)	1 (9.1)	
Stage at diagnosis, n(%)			0.798
II	17 (68.0)	7 (63.6)	
III	8 (32.0)	4 (36.4)	
Biological subtype, n (%)			0.363
Luminal HER2-	17 (68.0)	9 (81.8)	
Luminal HER2+	5 (20.0)	0 (0.0)	
HER2-enriched	1 (4.0)	1 (9.1)	
Triple negative	2 (8.0)	1 (9.1)	
Final surgery of the breast, n (%)			0.837
Breast-conserving surgery	15 (60.0)	7 (63.6)	
Total mastectomy	10 (40.0)	4 (36.4)	
Final pathology, n (%)			0.888
Benign	2 (8.0)	0 (0.0)	
In situ	4 (16.0)	1 (9.1)	
Invasive	19 (76.0)	10 (90.9)	
Histological type, n (%)			0.347
Ductal NST	16 (64.0)	7 (63.6)	
Lobular	2 (8.0)	1 (9.1)	
Mucinous	0 (0.0)	1 (9.1)	
Mixed NST + other	1 (4.0)	0 (0.0)	
Other	0 (0.0)	1 (9.1)	
Benign/*In situ*	6 (24.0)	1 (9.1)	
Histological grade, n (%)			0.482
1	2 (8.0)	0 (0.0)	
2	12 (48.0)	8 (72.7)	
3	5 (20.0)	2 (18.2)	
Unknown	0 (0.0)	0 (0.0)	
Benign/*In situ*	6 (24.0)	1 (9.1)	
ypT, n (%)			0.641
0	2 (8.0)	0 (0.0)	
In situ	4 (16.0)	1 (9.1)	
1A	1 (4.0)	0 (0.0)	
1B	3 (12.0)	0 (0.0)	
1C	7 (28.0)	3 (27.3)	
2	8 (32.0)	7 (63.6)	
3	0 (0.0)	0 (0.0)	
4	0 (0.0)	0 (0.0)	
Perineural invasion, n (%)			0.076
Yes	1 (4.0)	3 (27.3)	
No	24 (96.0)	8 (72.7)	
Lymph-vascular invasion, n (%)			0.008
Yes	4 (16.0)	7 (63.6)	
No	21 (84.0)	4 (36.4)	
Multifocality, n (%)			0.388
Yes	7 (28.0)	1 (9.1)	
No	18 (72.0)	10 (90.9)	
Number of CN excised, median (range)	1 (0-1)	0 (0-2)	0.456
Number of SN excised, median (range)	2 (1-3)	1 (1-4)	0.813

† Mann-Whitney U, Pearson's chi-squared test/Fisher's exact test.

of lymph-vascular invasion predicted additional NSLN involvement (p=0.008) (Table 4).

8. OVERALL SURVIVAL (OS) AND DISEASE-FREE SURVIVAL (DFS)

Concerning vital status, one (1.2%) patient died from BC, seven (8.2%) were alive with recurrence (two local, one regional and four distant recurrences) and 77 (90.6%) were alive with no evidence of recurrence (Table 5). There were no differences in OS (log rank p=0.928) or DFS (log rank p=0.177) between the four subsamples of patients (Figs. 3 and 4). There were no differences in OS (log rank p=0.270) between ALND and no-ALND patients (Fig. 5). DFS was significantly better in patients who did not perform ALND (log rank p=0.029) (Fig. 4).

Table 5 – Main outcomes according to axillary status and procedures

Patient serial number	Outcome	ycN status	First axillary procedure	Second axillary procedure
8	local recurrence	ycN0	TAD	ALND
16	distant recurrence	ycN0	TAD	ALND
16	death	ycN0	TAD	ALND
25	distant recurrence	ycN0	TAD	ALND
26	regional recurrence	ycN+	SLNB	ALND
28	distant recurrence	ycN0	TAD	Not performed
29	local recurrence	ycN0	TAD	Not performed
84	distant recurrence	ycN+	TAD	ALND

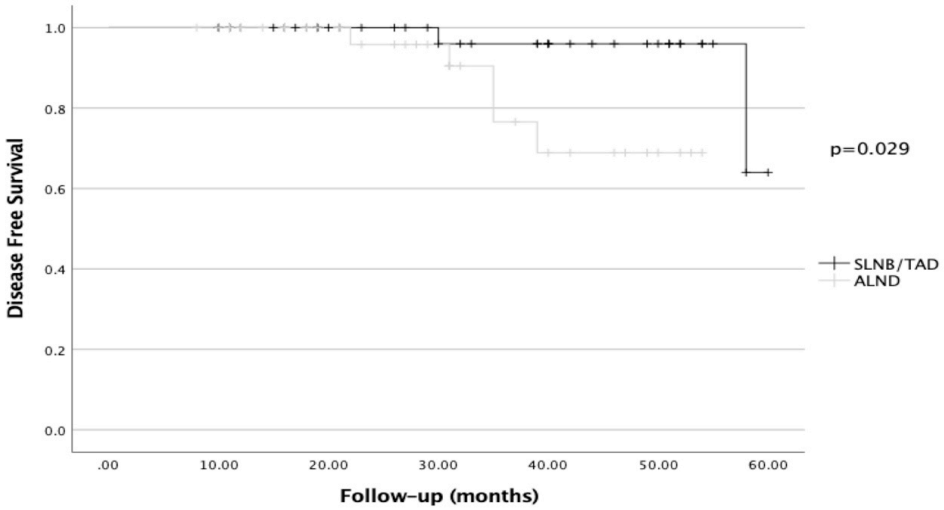

Figure 2 – Disease free survival in patients submitted to SLNB/TAD versus patients who performed ALND.

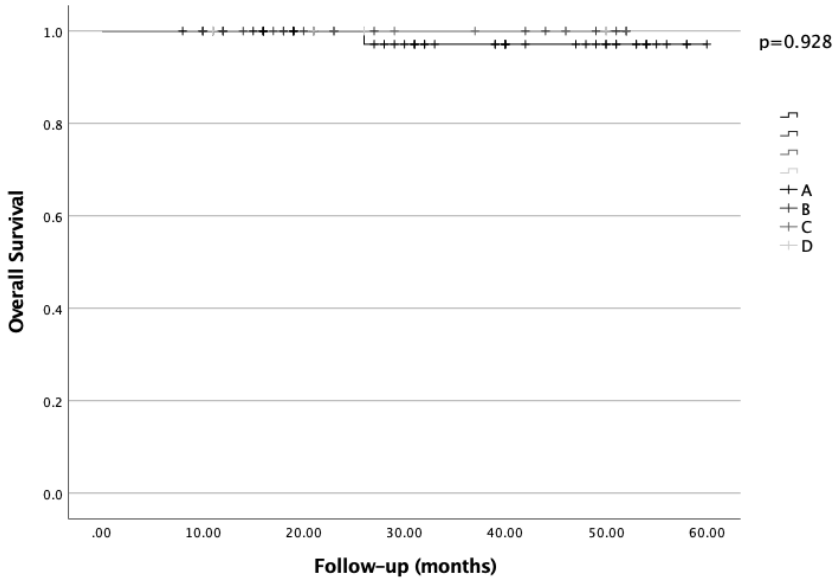

Figure 3 – Overall survival across groups.

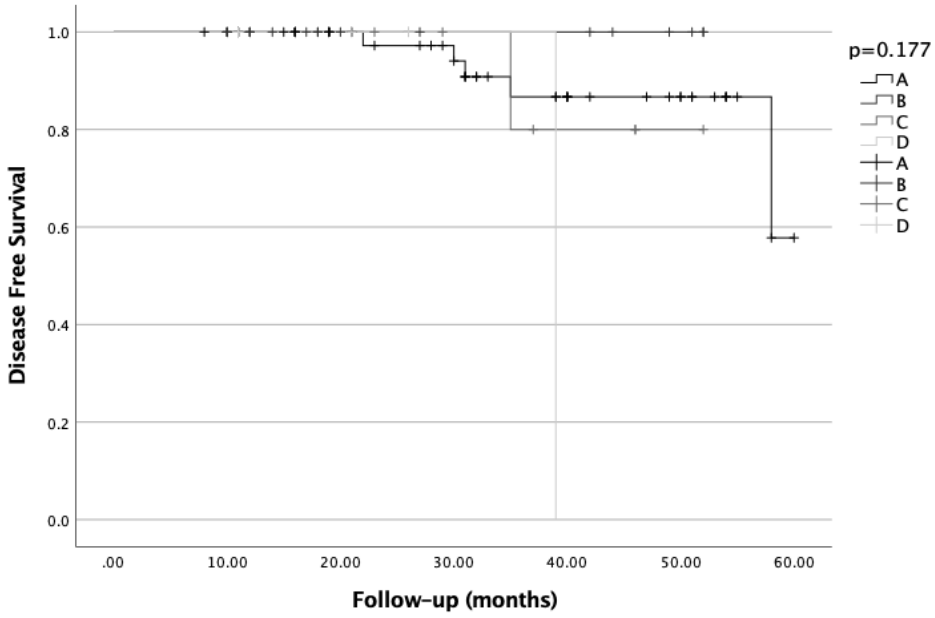

Figure 4 – Disease free survival across groups.

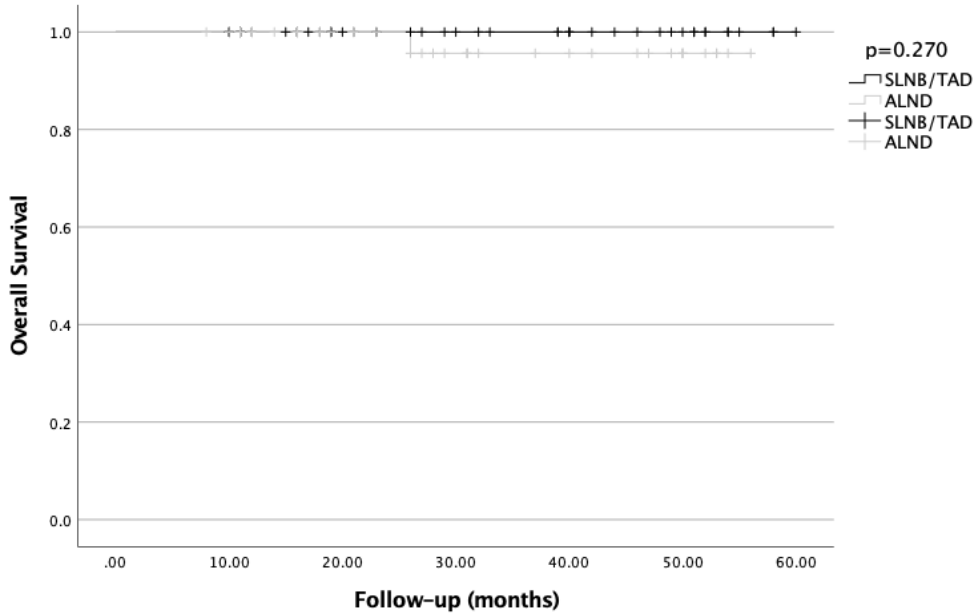

Figure 5 – Overall survival in SLNB/TAD patients *versus* ALND patients.

DISCUSSION

In our study, we compared SLNB using ICG and PBV with TAD (CNB+SLNB) in the setting of NAT in cT1-4c cN1-2 BC patients. Our results are best applicable to cT2 cN1 patients who converted to ycN0, as this was the majority of our sample.

DR was 83.6% for CNB (***vs*** 95.6% in the ILINA study[20]), 98.8% for SLNB and 98.8% for TAD (CNB+SLNB) patients. The relatively low DR obtained for CNB may reflect the learning curve associated with this procedure. CNB did not drive management changes as every CN was a SN. This is contrary to recent findings by Costarelli ***et al***,[35] where in 3% of patients only non-sentinel CN were identified. Their study relied on RI+PBV for SLNB. Results for SLNB after NAT in initially cN+ patients are conflicting as shown by a recent meta-analysis[36] where a pooled DR of 92.0% for RI, 96.0% for PBV, and 89% for RI+PBV was found. Nevertheless, our study compares favorably with all of these, with a SLNB DR of 98.8% using PBV+ICG, with at least three SN identified in 55.3% of the patients and with inclusion of both ycN0 and ycN+ patients. We cannot estimate the FNR of SLNB or TAD in our sample as only patients with an unsuccessful SLNB/TAD procedure or positive nodes proceeded to an ALND.

The use of indocyanine green can help secure removal of at least 3 SN.[37] In our study, the removal of three or more SN was associated with a successful CNB (p=0.001). Our findings are corroborated by a recent study in which when 3 or more SN were removed using a dual labeling technique, the CN was sentinel in the majority of cases. Also, in their study, 31 patients did not have a CN retrieved: in 13 patients there was a positive SN mandating ALND and in 18 with negative SN, no axillary recurrences were observed with a median follow-up time of 55 months.[38]

As shown in our study, an unsuccessful CNB can prompt more intra-operative time, additional imaging exams, re-operation (leading to increased morbidity[39]) and delay in the adjuvant treatments with no added benefit. The same issues were highlighted by Flores-Funes ***et al*** in their review paper.[40]

Correct identification of the SN, ***i.e.***, the first node(s) receiving the lymph drainage from the tumor, is vital to assess nodal pathological response and to decide which patients can be spared an ALND.[41,42] In our study, fewer suspicious nodes at diagnostic ultrasound, an aggressive biological subtype, pCR of the breast and absence of lymph-vascular invasion were significantly associated with SN pCR. These are factors commonly associated with nodal pCR[43] and we are confident that the nodes identified as SN in our study were the most informative ones. Therefore, this contributes to the validation of SLNB after NAT for axillary staging. Also, fewer suspicious nodes (1 ***vs*** >=2) at initial echography and aggressive biological subtype (HER2-positive or triple-negative) are factors available before surgery and useful to predict nodal pCR. We should underline the discordance between pCR rates in the

breast (41.2%) and in the nodes (50.6%). pCR discordance rates vary between 1.5%-30.0%, usually favoring the breast.[44,45] One possible explanation is that 64.7% and 21.2% of the patients in our sample had one and two suspicious nodes at diagnostic ultrasound, respectively. This reduced tumor burden in the axilla may explain the greater axillary response. Nonetheless, pCR of the breast was predictive of pCR in the nodes, a usual finding.[43]

Regarding the ycN+ patients in our sample, 4 (44.4%) Group C and 3 (50.0%) Group D patients had pathologically negative SN. In these cases, imaging exams showed suspicious architectural changes which could, in some centers, translate into direct ALND. Our results show that there is still benefit in staging the axilla using SLNB, because some of these patients will be SN negative and can skip further axillary surgery. ALND is a means for controlling regional disease and, in our sample, regional recurrence was a rare event, occurring in one (1.18%) SLNB+ALND patient with lobular carcinoma. In line with current practice, ypN0sn patients can skip ALND. However, ALND continues to be recommended for ypN+sn patients.[36] In our study, only a third of the ypN+sn patients had additional metastasized NSLN and lymph-vascular invasion in the primary tumor was predictive of NSLN involvement. Therefore, even some ypN+sn patients could be spared from ALND, if accurate prediction of NSLN involvement could be assured.[46] This should be investigated in future studies with bigger sample sizes and longer follow-up time.

Despite the short follow-up time and reduced sample size, there were no differences in OS or DFS between SLNB and TAD patients. Both these methods of staging the axilla are comparable in terms of oncological outcomes and this is confirmed in a study with longer follow-up time and bigger sample size.[47] All but one patient had a successful SLNB procedure. Considering all of the study sample, we compared SLNB-only *versus* SLNB followed by ALND. DFS was significantly worse in ALND patients, an expected finding as these were ypN+sn patients.[48] SLNB was also an adequate staging procedure, helping to define adjuvant treatment, as demonstrated by the absence of a significant difference in OS between SLNB-only and ALND patients. Nonetheless, this should be confirmed in prospective studies with longer follow-up times.

Our work showed that every clipped node was identified as a SLN and that the use of a dual labeling technique for SLNB allowed the retrieval of 3 SN, thus making CNB superfluous. Nonetheless, the recommendation for relying exclusively on SLNB in this context should be made when prospective studies with bigger samples that assess the oncological outcomes associated with this attitude are available. We confirmed that it is appropriate to omit ALND when the pCR of the SN obtained via SLNB is achieved. Future studies should assess the need for ALND in some ypN+sn patients.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available in accordance with ULS São João data protection requirements. Further inquiries can be directed to the corresponding author.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).
Provenance and Peer Review: Not commissioned; externally peer reviewed.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Disponibilidade dos Dados: Os conjuntos de dados gerados e/ou analisados durante o presente estudo não estão disponíveis ao público, de acordo com os requisitos de proteção de dados da ULS São João. Para mais informações, contactar o autor correspondente.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

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CONTRIBUTORSHIP STATEMENT

NS: Study concept, design; data acquisition, analysis and interpretation; statistical analysis; manuscript preparation, editing and review.

JF: Study concept; manuscript preparation, editing and review.

BP: Data acquisition; quality control of data and algorithms; manuscript editing and review.

CP: Manuscript editing and review.

All authors approved the final version to be published.

DECLARAÇÃO DE CONTRIBUIÇÃO

NS: Conceção e desenho do estudo; aquisição, análise e interpretação dos dados; análise estatística; preparação, edição e revisão do manuscrito.

JF: Conceção do estudo; preparação, edição e revisão do manuscrito.

BP: Aquisição de dados; controlo de qualidade dos dados e algoritmos; edição e revisão do manuscrito.

CP: Edição e revisão do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

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