Original Article

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Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy in cN0 Breast Cancer: Impact of HER2-Positive Status on Survival

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ABSTRACT

Objective: High rates of negative sentinel lymph node biopsy (SLNB) in clinically node-negative (cN0) breast cancer (BC) after neoadjuvant chemotherapy (NAC) have been described. These results are associated with triple-negative (TNBC) and human epidermal growth factor receptor 2 (HER2+) subtypes achieving pathologic complete response (pCR). This study evaluates predictive variables and survival in order to assess the possible omission of SLNB after NAC.

Materials and Methods: Prospective study of women with cN0 BC treated with NAC and subsequent surgery, between April 2010 and May 2021. SLNB technique included, performing axillary lymphadenectomy in the absence of detection or SLNB-positivity. Multivariable logistic regression was used for analysis of NAC-response and SLNB-results in molecular subtypes: HR-/HER2+, TNBC, HR+/HER2- and HR+/HER2+. Kaplan-Meyer and log-rank were used for survival analysis.

Results: A total of 179 patients (50.5±10.1 years) were included. Of these, 39.7% achieved pCR (ypT0/Tis). HR-negative subtypes had higher pCR rates (HR-/HER2+: 59.4%; TNBC: 53.4%), with no cases of SLNB-positive. With residual disease, HR-/HER2+ and TNBC showed low rates of SLNB-positivity (6.7% and 10.3%) versus HR+ (HR+/HER2+: 20%; HR+/HER2-: 44%; $p<0.001$). Multivariable analysis identified independent predictors of SLNB-negativity ($p<0.0001$) to be: HR- [odds ratio (OR)=0.15; 95% confidence interval (CI): 0.06–0.37; $p = 0.0001$], HER2+ (OR=0.34; 95% CI: 0.14–0.81; $p = 0.015$) and high-grade Nottingham (OR=0.42; 95% CI: 0.18–0.99; $p = 0.048$). Disease-free survival showed worse outcomes with SLNB-positivity ($p<0.0001$), HR+/HER2- ($p = 0.0277$), larger tumor size ($p = 0.002$) and residual disease after NAC ($p<0.0001$).

Conclusion: Patient selection based on NAC response, molecular subtype, and survival outcomes is a priority for establishing individualized therapeutic strategies after NAC. Molecular subtypes with higher pCR rates and lower rates of SLNB-positivity could benefit from non-invasive strategies that include omission of SLNB.

Keywords: HER-2/neu; neoadjuvant chemotherapy; sentinel lymph node biopsy; survival; triple negative breast cancer

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Key Points

- SLNB after NAC safe and effective treatment for cN0.
- Molecular subtype tumor size predictors pCR.
- NAC response strongest prognosis predictor.
- SLNB-negative pCR achieved better prognosis.
- HER2+ benefit omission SLNB technique.

Introduction

Sentinel lymph node biopsy (SLNB) in breast cancer (BC) is a validated tool for axillary staging after neoadjuvant chemotherapy (NAC) in patients with clinically negative nodes (cN0) (1). Tumor size and BC molecular subtype are important predictors of NAC-response (2). cN0 patients with triple-negative (TNBC) and human epidermal growth factor receptor 2 (HER2+) BC show high rates of SLNB-negativity (ypN0) (3-5). Patients with a pathological complete response (pCR) show higher disease-free survival (DFS) and overall survival (OS) (6). SLNB after NAC allows better assessment of response to NAC (7-9). Molecular subtypes are important for

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predicting SLNB-negativity with high probability of pCR. There is no standard that recommends omitting axillary surgery in cN0 patients undergoing NAC (10). There are currently several ongoing trials (11), including two prospective trials that aim to assess axillary recurrence-free survival (ARFS) when omitting SLNB after NAC in patients initially diagnosed as cN0 (12, 13). This study presents the survival outcome of a cohort of patients who received NAC, with the aim of providing data for the omission of axillary surgery in selected cases.

Materials and Methods

Between April 2010 and May 2021, 179 women were retrospectively and consecutively included in the study. All patients and their associated data originate from a single healthcare institution: the 'Hospital Clínico Virgen de la Victoria' in the city of Malaga, Spain. It is a first-level hospital, a reference center in BC treatment that provides care to a population of 500,000 inhabitants. The following inclusion criteria were established: Age between 18 and 80 years, newly diagnosed invasive breast carcinoma, clinically negative axilla and/or confirmed through Fine-Needle Aspiration Biopsy (FNAB), undergoing complete SLNB technique with a dual tracer, receiving NAC consisting of Anthracyclines + Taxanes or Cyclophosphamide, receiving adjuvant chemotherapy after surgery, receiving local and axillary radiotherapy after surgery, and receiving Trastuzumab and/or Pertuzumab in HER2-positive patients, as well as hormonal therapy in hormone receptor-positive patients.

Exclusion criteria comprised; age >80 years, as international guidelines did not clarify the use of SLNB in this age group at the beginning of the study; history of previous neoplasia, either BC or any other origin; development of a new neoplasia of a different origin than breast; positive metastasis in the biopsy of a suspicious lymph node by FNAB; any other chemotherapy regimen not mentioned in the inclusion criteria; absence of radiotherapy treatment; absence of hormonal treatment if required; and absence of anti-HER2 treatment if required (Figure 1).

The initial anatomopathological diagnosis of the tumor was performed on samples obtained by core needle biopsy. The material was immediately fixed in buffered neutral formalin and embedded in paraffin. Three-millimeter sections were stained with hematoxalin and eosin (H&E) and macroscopically analyzed for tumor type and histological grade, which adhered to the Nottingham (Scarff-Bloom-Richardson) system. Subsequently, an immunohistochemical analysis was performed to define the molecular subtype.

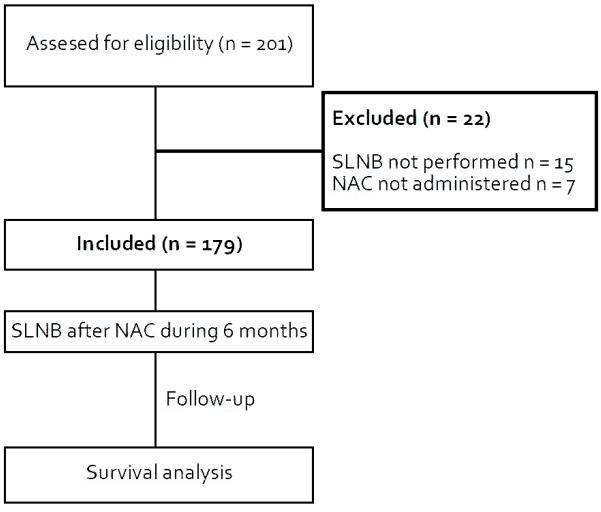

Figure 1. CONSORT flow diagram

SLNB: Sentinel lymph node biposy; NAC: Neoadjuvant chemotherapy

The criteria for NAC indication in cN0 BC patients have been based on the presence of HER2+ or TNBC subtypes and/or the accepted indication for reducing tumor volume to enable more conservative surgery. These NAC indications have been determined by a multidisciplinary team and have been crucial in evaluating the chemotherapy response in these specific cases, thus contributing to establishing a well-defined patient cohort.

SLNB technique was performed by intradermal periareolar injection with 37 MBq of 99mTc-nanocolloid of human serum albumin (Nanocoll®) for lymphoscintigraphy. Intraoperative localization of SLN was performed with gamma probe by an experienced Nuclear Medicine specialist.

During the intraoperative examination, both the tumor and sentinel lymph nodes (SLNs) were promptly sent to the Pathology Department for further analysis. A skilled pathologist conducted a macroscopic evaluation of the lymph node and subsequently sectioned it longitudinally/vertically based on its morphology, creating sections that were 2 mm thick. The most suspicious section, identified macroscopically, was frozen at -20 °C and later cut into 5–10 micrometer-thick sections, which were stained with H&E to assess malignancy. This procedure took approximately 15–25 minutes.

Following the intraoperative assessment of the SLNs, the definitive histopathological study of the tumor and SLN was performed. The tumor was processed with 3-millimeter sections in blocks, and an immunohistochemical study was conducted in separate blocks. Each lymph node was individually fixed in formalin and embedded in separate paraffin blocks. From each block, two 3-micrometer sections were obtained, with an interval between them of 3–5 micrometers, and subsequently stained with H&E. Tumor and lymph node involvement were defined according to the American Joint Committee on Cancer (AJCC - 8th edition) Breast Cancer Staging standard (14) and the Residual Cancer Burden (RCB; MD Anderson Cancer Center, Houston, Texas, USA) (15). This comprehensive approach allowed for accurate assessment and characterization of the NAC response, contributing to the robustness of the study's findings. Isolated tumor cells, micrometastases, and macrometastases were considered as tumor presence at the lymph node level. The cases from our series evaluated through the Miller and Payne system, before the development of Symmans' RCB system, were reevaluated and assigned an RCB index and class and *yp* stage for a correct evaluation of the series. Axillary lymph node dissection (ALD) was performed with intraoperative SLNB-positive and with definitive positive results.

Clinical follow-up after surgery was scheduled every 6–12 months for a period of at least five years.

Statistical Analyses

Clinical variables were prospectively recorded and evaluated with parametrical or non-parametrical test according to appropriateness. Our hypotheses included assessing survival outcomes (DFS, OS, and ARFS) after NAC and identifying predictive factors for negative SLNB results in patients achieving a pCR. The primary outcome was OS, with secondary outcomes including DFS and ARFS. The study's variables encompassed patients' demographics, clinical characteristics,

tumor subtypes, NAC response, and corresponding outcomes, which were analyzed. For OS and DFS Kaplan-Meier analysis and the log-rank test were used. For all analyses, SPSS, version 22 for Windows was used (SPSS, Inc., Chicago, IL, USA).

Results

The clinical characteristics of the patients are shown in Table 1. Most frequent NAC protocol was anthracyclines and taxanes (n = 156; 87.2%), including docetaxel and cyclophosphamide/carboplatin,

Table 1. Patient and tumour characteristics

Variable	No. of patients*
Total number of patients	179 (100.0)
Age, in years [SD; range]	50.5‡/49.9† (±10.1; 29–77)
Body mass index, kg/m²	
<18.5	2 (1.1)
18.5-24.9	74 (41.3)
25-29.9	55 (30.7)
≥30	42 (23.5)
NA	6 (3.4)
Menopausal status	
Premenopausal	88 (49.2)
Perimenopausal	16 (8.9)
Postmenopausal	75 (41.9)
Tumor size, in mm [± SD; range]	33.2‡/30† [±13.7; 10–100]
cT stage	
T1	24 (13.4)
T2	135 (75.4)
T3	14 (7.8)
T4	6 (3.4)
c-Stage	
I	24 (13.4)
IIA	113 (75.4)
IIB	14 (7.8)
III	6 (3.4)
Hystological type	
Ductal invasive NST	165 (92.2)
Lobular invasive	6 (3.4)
Metaplasic invasive	4 (2.2)
Mucious invasive	2 (1.1)
Apocrin invasive	2 (1.1)
Laterality	
Right breast	98 (54.7)
Left breast	81 (45.3)
Location	
External	83 (46.4)
Internal	33 (18.4)
Center	37 (20.7)
Multifocal	26 (14.5)
Nottingham grade	
1	8 (4.7)
2	61 (35.9)
3	101 (59.4)
Surgical procedure	
Lumpectomy	154 (86)
Mastectomy	25 (14)
Hormone receptor (HR)	
Positive	89 (49.7)
Negative	90 (50.3)
HER2-neu receptor (HER2)	
Positive	77 (43)
Negative	102 (57)
Molecular subtypes	
HR-/HER2+	32 (17.9)
HR+/HER2+	45 (24.6)
HR+/HER2+	44 (25.1)
TNBC	58 (32.4)
Pathological response (RCB symmans)	
pCR	69 (38.5)
RCB-I	17 (9.5)
RCB-II	79 (44.1)
RCB-III	14 (7.8)
ypT category after NAC	
ypT0	52 (29.1)
ypTis	19 (10.6)
ypTmi	2 (1.1)
ypT1	57 (31.8)
ypT1a	3
ypT1b	14
ypT1c	40
ypT2	44 (24.6)
ypT3	5 (2.8)
ypN category after NAC	
ypN0	140 (78.2)
ypN0(i+)	6 (3.4)
YpN1mi	5 (2.8)
YpN1a	18 (10.2)
ypN2	6 (3.4)
ypN3	1 (0.6)
Pathology of SLNs	
Tumour-negative	140 (79.5)
Tumour-positive	36 (20.5)
Macrometastasis	25 (14.2)
Micrometastasis	5 (2.8)
ITCs	6 (3.4)
Follow-up, in months [SD; range]	50.9‡ / 45.3† [± 29.3; 12–124]
Progression during NAC	1 (0.6)
Global recurrence	21 (11.7)
Locoregional recurrence	11 (6.1)
Distant recurrence	17 (9.5)
Decreased	10 (5.6)

*With percentages in parentheses unless indicated otherwise; values are ‡mean and †median with [± SD, range]. NST: No special type; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; TNBC: Triple negative breast cancer; NAC: Neoadjuvant chemotherapy; pCR: Pathological complete response; SLN: Sentinel lymph node; ITC: Isolated tumour cell; SD: Standard deviation

palbociclib or T-DM1. HER2 therapy and hormone therapy were used, if indicated. Breast surgery was performed six months after NAC. Median (range) time between diagnosis and NAC was 36 (14–67) days and mean NAC was 5.9±1 months. SLN-negatives (n = 140) not submitted to ALD were followed from diagnosis for a mean of 51±29 months with no case of axillary involvement. There were 36 cases which were SLNB-positive [HR+: 28 (77.8%), TNBC: 6 (16.7%) and HER2+/HR-: 2 (5.5%)] and in three cases ALD was performed due to SLNB non-detection.

In total 71 patients (38.5%) had breast pCR (Table 2) and higher rates was obtained in HER2+ (p = 0.046) and HR- (p<0.0001). HR+/HER2- was associated with breast pCR in 6.8%, compared to 59.4% in HR-/HER2+ and 53.4% TNBC patients (p<0.001). Significant predictors of pCR were HR- (p<0.0001), Nottingham score (p = 0.0013), HER2+ (p = 0.05), and cT/tumour size (p = 0.04/p = 0.0018). HR- (p = 0.0006) and HER2+ (p = 0.0087) were independent predictors of pCR (Table 3).

The most frequent molecular subtype in the 36 patients with *yp*N+ status (20.5%) was HR+ (77.8%). Breast pCR was a significant predictor of SLNB-negativity (97.2%; p<0.001). The strongest predictors of *yp*N0 before surgery were molecular subtype (p<0.001), tumour size (p = 0.005), and Nottingham score (p = 0.003) (Table 4).

Disease progression occurred in 21 (11.7%), subdivided into local recurrence (n = 11; 6.15%), and disseminated disease (n = 16; 8.93%). Mean time from surgery to local recurrence was 25±17 months,

Table 2. Pathological response of breast to primary systemic therapy

NAC response (RCB)		**n**	**(%)**
pCR - Complete response (ypT0/Tis)		69	(38.5)
pCR with axillary involvement			
	ypN0(i+)	2	(1.1)
Partial response or no response		108	(60.3)
	ypT1	57	(31.8)
	ypT2	44	(24.6)
	ypT3	5	(2.8)

NAC: Neoadjuvant chemotherapy; pCR: Pathological complete response; RCB: Residual Cancer Burden

Table 3. Univariable and multivariable analysis of predictors of pathologic complete response with their pathologic complete response rates

	% pCR	**Univ. (p-value)**	**Multiv. (p-value)**	**Multiv. OR**	**95% CI for OR**	
					Lower	**Upper**
Tumor size						
≤30	49.46	0.0018	0.0102	1.8136	0.8889	3.7002
>30	26.74					
ki-67						
Value >20	45.86	0.0008	0.1239	2.2066	0.8051	6.0480
Value ≤20	17.78					
Grade						
3	47.52	0.0013	0.0834	2.0246	0.9111	4.4989
1-2	23.19					
HR						
Negative	54.44	0.00001	0.0006	3.8019	1.7784	8.1281
Positive	22.47					
HER2						
Positive	46.75	0.046	0.0087	2.7446	1.2913	5.8333
Negative	32.35					
Multivariable analysis = X2=38.76; p<0.0001						

pCR: Pathologic complete response; OR: Odds ratio; cT-stage: Clinical tumor stage; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; CI: Confidence interval; Multiv.: Multivariable; Univ.: Univariable

disseminated disease 26±17 months and *exitus* 38.7±18 months. Death occurred in 10 cases so that OS was 90.6%. In pCR, the OS at 5 years was 100% (non-pCR 84.2%; p = 0.007). DFS showed significant differences regarding SLNB (p<0.0001), HER2 expression (p = 0.0277), tumour size (p = 0.002), and NAC-response (p<0.0001) (Figure 2).

Discussion and Conclusion

SLN identification reached the recommended value of at least 95% (16, 17). Periareolar intradermal injection can obtain better radiotracer drainage compared to intra- or peritumoral injections. It is important to highlight the absence of axillary recurrence (AR) in the cases of negative SLNB, in line with previous publications (18-20)

Table 4. Univariable analysis of predictors for negative sentinel lymph nodes after NAC

			No. of patients	Negative SLN	Negative SLN rate (%)	*p*-value
All patients			179	140	79.5	
Histology						0.166
Invasive cancer, NST			165	131	80.9	
Invasive lobular cancer and others**			14	9	64.3	
Tumour subtype						<0.001
HR-/HER+			30	28	93.3	
HR+/HER+			45	36	80	
TNBC			58	52	89.7	
HR+/HER2-			43	24	55.8	
Nottingham Grade						0.003
I and II			68	46	67.6	
III			101	86	86.9	
Unknown			9			
cT-stage						0.117
cT1			24	22	91.7	
cT2			132	103	78	
cT3			14	12	85.7	
cT4			6	3	50	
T size						0.005
≤30 mm			92	81	88	
>30 mm			84	59	70.2	
Tumour focality						0.430
Unifocal			150	121	80.7	
Multifocal/multicentric			26	19	73.1	
ypT category after NAC						<0.001
	pCR		71	69	97.2	
		ypT0	52	51	98.1	
		ypTis	19	18	94.7	
	ypT1		57	40	70.2	
		ypT1mi	2	2	100	
		ypT1a	2	1	50	
		ypT1b	13	11	84.6	
		ypT1c	40	26	65	
	ypT2		43	28	65.1	
	ypT3		5	3	60	

SLN: Sentinel lymph node; NST: No special type; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; TNBC: Triple-negative breast cancer; NAC: Neoadjuvant chemotherapy; pCR: Pathological complete response. *metaplasia (4), mucinous (2) and apocrin (2)

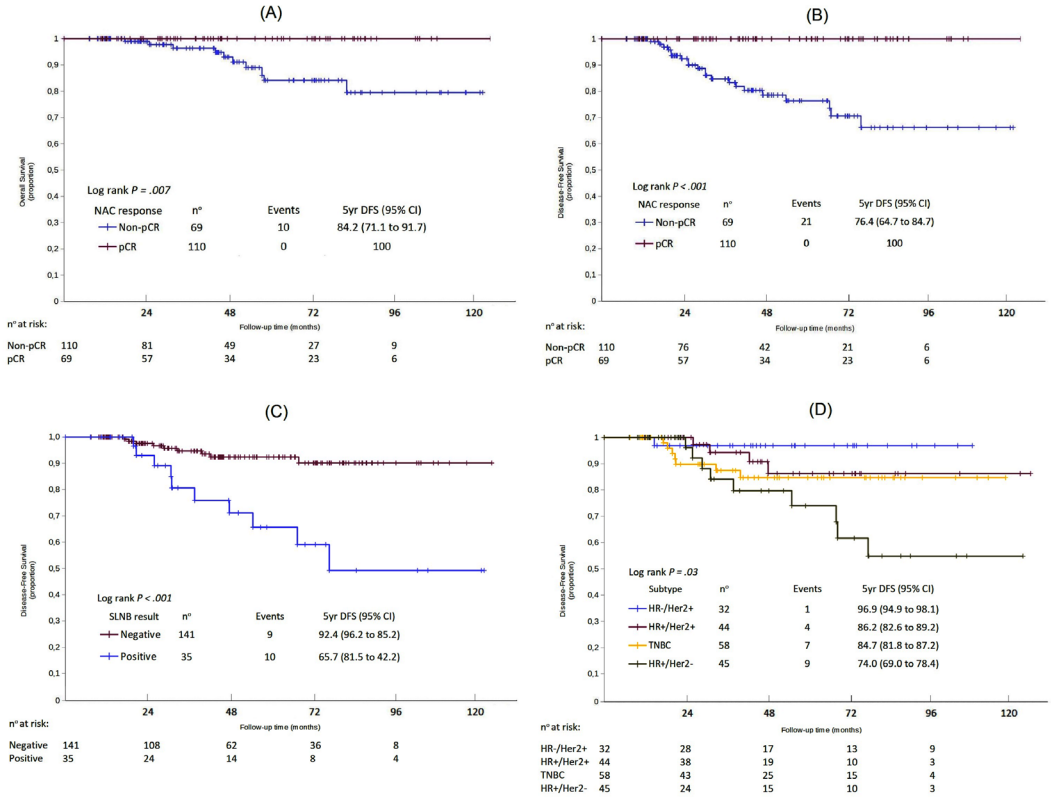

Figure 2. (A) Overall survival (OS) (y-axis) and **(B)** disease-free survival (DFS) (y-axis) plotted against time in months from cancer diagnosis (x-axis) according to NAC-response groups: pCR (red) and residual-disease (blue). **(C)** DFS (y-axis) plotted against SLNB-result: Negative (red) and positive (blue). **(D)** DFS (y-axis) plotted against tumour molecular subtypes: HR-/HER2+ (blue), HR+/HER2+ (red), TNBC (yelow) and HR+/HER2- (green). Log-rank P values for each survival graph are shown.

SLNB: Sentinel lymph node biposy; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; TNBC: Triple-negative breast cancer; NAC: Neoadjuvant chemotherapy; pCR: Pathological complete response

suggesting that SLNB performs better than ALD. We do not attribute this to the average length of follow-up, which was longer than in other published studies (34 months) (21), nor to the interval of time until AR. Another reason for the absence of AR was the use of adjuvant systemic treatment, which lowers the risk for local and regional recurrence (22, 23). In the present study, patient selection was based on the chemotherapy course, in which all patients received hormone and anti-HER2 therapy depending on the molecular subtype, NAC was based on anthracyclines and taxanes in 91.6% of cases, of which only 5% did not complete treatment. The increase in the rate of local recurrence in these cases of high fibrosis due to good response to NAC, which translates into pCR, is a matter of concern for surgeons. In our study, we had no recurrence is any patient achieving pCR.

Tumor size and molecular subtypes are independent predictors of pCR (18-21). Some authors claim that achieving pCR does not completely rule out long-term recurrence. Thus, for the design of our study we took into account the limitation of previous studies (retrospective nature, lack of knowledge of NAC courses, Nottingham scoreing, and pathological data) to evaluate the survival results. We found an OS and a DFS at five years of 100% in the group that achieved pCR, independently of the tumour size at diagnosis and the molecular subtype. The strengths of these results lie in the well-selected patient sample, with a high homogeneity of chemotherapy scheme and an exhaustive registry of the administered cycles and the causes for treatment interruption. The presence of HR+ could negatively influence the pCR rate of the HER2+ group, whereas HR-/HER2+ achieves higher pCR rates, with impact on NAC response and OS/DFS. OS and DFS were 100% in the pCR group, probably due to well-selected patients, with homogeneous NAC protocols and anti-HER2 therapy. Furthermore, and according to literature, there could be a slight difference in prognosis with respect to the *in situ* presence of tumour after NAC (24, 25). Based on this evidence, another strength of our study is the registry of all variables of the pathological examination of the samples, which provided exact data on staging of the AJCC and RCB of Symmans after NAC. We obtained an OS and a DFS at five years of 100% in the group of women who had an *in situ* component in the samples that corresponded to the ypTis stage and the pCR category. Therefore, in our study, these women showed the same excellent results regarding OS and DFS at five and eight years as those achieving a complete pCR, categorized as ypT0.

It is worth highlighting that in our study the DFS at five years for our TNBC group, considered as a good response to NAC (pCR rate of 51.7%) was 84.7%, whereas the DFS at five and eight years for the HR+/HER2- group was 73.3% and 54.3%, with a pCR rate of only 6.8%. We explain this notable prognosis difference between groups, compared to other studies (20) by homogeneity in the NAC courses, with subsequent adjuvant chemotherapy.

Current evidence suggests that molecular criteria should be prioritized over anatomical criteria, especially in higher probability of recurrence in patients with HR+ tumours (26-28). Our OS and DFS results in the HR+/HER2- subtype suggest considering an initial surgery and a later

adjuvant treatment, omitting NAC, with the objective of removing the biggest amount of tumour tissue with low probability of response to chemotherapy as soon as possible.

Predictive factors of SLNB would permit the patient selection for omission of SLNB after NAC.

A limitation of this study is that magnetic resonance imaging was not performed (29), without radiologic complete response assessment. Nonetheless, results regarding the association of RCB index and molecular subtype show its value as a predictive tool for breast pCR and negative-SLNB rate. Significant rates of ypN0 in HR-/HER2+ and TNBC, compared to HR+ show molecular subtype as an initial criterion to select patients for omission of SLNB after NAC. Tumour subtype and breast pCR were the strongest predictive characteristics in SLNB-negativity after NAC. Omitting SLNB could be an option in TNBC and HR-/HER2+ who achieve breast pCR, with the support of correct assessment with imaging techniques (30).

The findings of this study affirm that SLNB after NAC is an appropriate, safe and effective treatment for cN0. The most important predictors of pCR were molecular subtype and tumor size. Response to NAC is the strongest predictor with better prognosis if SLNB-negativity and pCR are achieved. A categorization of molecular subtypes based on response to NAC, SLNB and survival is a priority to establish individualized therapeutic strategies after NAC. Molecular subtypes with higher pCR rates and lower SLNB-positivity rates could benefit from non-invasive axillary evaluation strategies that include omission of SLNB.

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Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: J.A.-R., S.S.-V., F.J.F.-G.; Concept: J.A.-R., S.S.-V., F.S.-P.; Design: J.A.-R., S.S.-V., F.S.-P.; Data Collection and/or Processing: J.A.-R., S.S.-V., F.J.F.-G.; Analysis and/or Interpretation: J.A.-R., S.S.-V., F.J.F.-G., F.S.-P.; Literature Search: J.A.-R., S.S.-V.; Writing: J.A.-R., S.S.-V., F.J.F.-G., F.S.-P.

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