Original Article

Nodal Response After Neoadjuvant Chemotherapy and Potential Targets for Axillary Surgery De-Escalation in Breast Cancer Patients

Resposta Ganglionar Após Quimioterapia Neoadjuvante e Potenciais Alvos para Descalar Cirurgia Axilar em Doentes com Cancro de Mama

Beatriz Pereira Gonçalves[1]*, Beatriz Costeira[1], Maria do Carmo Girão[2], Rodrigo Oom[1], Cristina Sousa Costa[1], João Vargas Moniz[1], Nuno Abecasis[1], Catarina Rodrigues dos Santos[3]

1. Department of General Surgery, Instituto Português de Oncologia de Lisboa Francisco Gentil (IPOLFG), Lisboa, Portugal
2. Department of General Surgery, Unidade Local de Saúde Baixo Alentejo, Beja, Portugal
3. Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal

Corresponding Author/Autor Correspondente:
Beatriz Gonçalves [beatrizmpgoncalves@gmail.com]
R. Prof. Lima Basto, 1099-023 Lisboa, Portugal

https://doi.org/10.34635/rpc.1106

ABSTRACT

Introduction: Neoadjuvant chemotherapy (NAC) has the potential for tumor downstaging and surgery de-escalation. In the axilla, this approach is less established, especially in cN+→ycN0. Targeted axillary dissection is an option, but difficult to concretize. We aim to identify biological factors associated with nodal pathological complete response (pCR) and recognize potential candidates for a more conservative axillary approach after NAC, such as sentinel lymph node biopsy (SLNB).

Received/Recebido: 11/06/2025 **Accepted/Aceite:** 12/08/2025 **Published online/Publicado online:** 21/10/2025 **Published/Publicado:** 09/12/2025

Methods: Retrospective, single-center cohort of patients with node-positive breast cancer, treated with NAC followed by axillary lymph node dissection from 2017 to 2021. The primary outcome was nodal pCR, overall and by molecular subtypes. A logistic regression model was conducted to identify biological factors predicting nodal pCR.
Results: A total of 414 patients were included. Overall, the nodal pCR rate was 37.9%. It was higher in HR+/HER2+ (62.1%), HR-/HER2+ (61.0%) and HR-/HER2- (56.3%) tumors, whereas only 21.6% in HR+/HER2- (p<0.001). In patients without nodal pCR, HR+/HER2- had the highest median number of positive lymph nodes (p=0.038). In multivariate analysis, HR+/HER2+ (OR 5.157, 95% CI 2.768-9.608, p<0.001), HR-/HER2+ (OR 4.207, 95% CI 1.935-9.147, p<0.001), HR-/HER2- (OR 2.242, 95% CI 1.180-4.261, p=0.014), and differentiation grade 3 (OR 4.075, 95% CI 2.448-6.784, p<0.001) were independently associated with nodal pCR.
Conclusion: Our data reveal HER2+, triple-negative and grade 3 tumors as predictive factors for nodal pCR. Parallel to the breast, axillary surgery de-escalation may be guided by tumor intrinsic factors. Identifying these "good responders" could help identify the candidates for a simpler axillary approach after NAC, such as SLNB.

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

RESUMO

Introdução: A quimioterapia neoadjuvante (QTNA) tem o potencial de *downstaging* tumoral, permitindo descalar cirurgia. Esta abordagem é menos estabelecida na axila, sobretudo em doentes cN+→ycN0. A linfadenectomia axilar seletiva é uma opção, mas difícil de concretizar. Pretendemos identificar fatores biológicos associados a resposta patológica completa (pCR) ganglionar e reconhecer potenciais candidatos para uma abordagem axilar após QTNA mais conservadora, como a biópsia do gânglio sentinela (BGS).
Métodos: Coorte retrospetiva unicêntrica de doentes com carcinoma da mama cN+, tratados com QTNA e linfadenectomia axilar de 2017 a 2021. O *outcome* primário foi a pCR ganglionar, global e por subtipo molecular. Foi desenvolvido um modelo de regressão logística para identificar fatores preditivos de pCR ganglionar.
Resultados: Incluídos 414 doentes. A pCR ganglionar global foi de 37,9%. Foi superior nos subtipos HR+/HER2+ (62,1%), HR-/HER2+ (61,0%) e HR-/HER2- (56,3%), e apenas 21,6% nos HR-/HER2- (p< 0,001). Entre aqueles sem pCR ganglionar, os HR+/HER2- apresentaram o maior número de gânglios positivos (p=0,038). Os subtipos HR+/HER2+ (OR 5,157; IC 95% 2,768–9,608; p<0,001), HR-/HER2+ (OR 4,207; IC 95% 1,935–9,147; p<0,001), HR-/HER2- (OR 2,242; IC 95% 1,180–4,261; p=0,014) e os tumores G3 (OR 4,075; IC 95% 2,448–6,784; p<0,001) associaram-se de forma independente com a pCR ganglionar.
Conclusão: Os tumores HER2+, triplo negativos e G3 foram identificados como fatores preditivos de pCR ganglionar. Paralelamente à mama, a biologia tumoral pode guiar o descalar da cirurgia axilar. A identificação destes "bons respondedores" poderá contribuir para selecionar candidatos a abordagens axilares mais conservadoras após QTNA, como a BGS.

Palavras-Chave: Biópsia de Gânglio Sentinela; Excisão de Gânglio Linfático; Gânglio Linfático; Neoplasias da Mama/cirurgia; Terapia Neoadjuvante

INTRODUCTION

This is the era of surgical de-escalation. The use of neoadjuvant chemotherapy (NAC) is increasing and now plays a crucial role in breast cancer treatment. It has the potential of tumoral downstaging, supporting the trend towards more conservative surgery. Additionally, the pathological response carries prognostic significance and allows for the evaluation of in vivo chemosensitivity.

In the breast, NAC increases the rate of breast-conserving surgery (BCS) by up to 40%.[1] However, in the axilla, this de-escalation approach is less established. Over the past 20 years, sentinel lymph node biopsy (SLNB) has become the gold standard for clinically negative axilla, both in upfront surgery and after NAC, reducing the need for axillary lymph node dissection (ALND) and, consequently, its associated morbidity. However, ALND remains the standard practice for

ycN+ cases after NAC. The challenge lies in cN+ tumors that convert to ycN0 following NAC, where some prospective studies report a false-negative rate (FNR) for SLNB exceeding the acceptable threshold of 10%.[2-5] To minimize this risk, strategies such as targeted axillary dissection (TAD) have been developed. TAD involves excising the previously marked metastatic lymph node along with the SLNB[6-8] and is recommended by multiple international guidelines as an option for this patient group.[9,10]

Although TAD is considered comparable to SLNB in terms of low morbidity rates, it requires a series of technical procedures that are often challenging to perform in hospital settings due to logistical constraints. Additionally, several issues remain unresolved, including the optimal number of nodes to be clipped, the potential of clip migration, the variability in how the positive clipped lymph node is labeled, and its retrieval during surgery.

It is well known that the pathological response to NAC varies among molecular subtypes, with higher rates of pathological complete response (pCR) observed in HER2+ and triple-negative subtypes.[11,12] Furthermore, the feasibility of a "no surgery" or "watch-and-wait" strategy in these patients is currently being investigated through ongoing prospective trials.[13] Given that nodal pCR is also influenced by tumor biology,[14-16] we aim to identify molecular subtypes associated with nodal pCR and determine which ones are potential candidates for a more conservative axillary approach after NAC, such as SLNB. Additionally, we seek to identify other biological factors associated with nodal pCR.

METHODS

From January 1st 2017 to December 31st 2021, all patients were retrospectively assembled from Instituto Português de Oncologia de Lisboa (IPOLFG) Breast Surgery Unit's prospective database. Patients with biopsy-proven, primary invasive, node-positive breast carcinoma who underwent ALND after NAC were included in the analysis. cT4 tumors, which require ALND regardless of cN status, were excluded. In patients with bilateral breast cancer, each tumor/surgery was considered an individual event.

The Ethics Committee of Instituto Português de Oncologia de Lisboa Francisco Gentil (IPOLFG) approved this study (UIC/1762) and granted an exemption from obtaining Informed Consent due to its retrospective design and non-interventional nature.

Preoperative local staging included breast magnetic resonance imaging (MRI) for all patients, both before and after NAC, unless contraindicated. Systemic staging included chest radiography, abdominal ultrasound, and bone scintigraphy. The treatment strategy for each patient was determined in a dedicated multidisciplinary breast cancer meeting, following institutional protocols. During the study period, HER2 blockade was performed using trastuzumab (Herceptin®). ALND was the standard axillary approach for all cN+ patients after NAC, regardless of axillary response. All surgical procedures were performed by breast-dedicated surgeons.

The analyzed variables included: patient demographics (age, gender, and genetic risk factors); tumor characteristics (histologic type, receptor status, differentiation grade, proliferative index Ki67, and clinical staging according to TNM [17]); imaging response after NAC (iCR), with tumoral iCR defined as the absence of residual enhancement and nodal iCR as the absence of suspicious axillary characteristics (thickened cortex, enhancement, loss or disruption of the central fatty hilum, irregular outer margins) on post-NAC MRI; technical aspects of surgery, including type of breast surgery and reconstruction details, if applicable; and pathology findings, including pathologic staging according to TNM [17] and quantification of lymph node involvement.

The primary outcome, *nodal pCR*, was defined as the absence of invasive disease in the axilla. Isolated tumor cells (i) in the axilla were considered invasive disease. Tumoral pCR was defined as the absence of invasive disease in the breast, with ductal carcinoma in situ (DCIS) still considered pCR. Global pCR was defined as the simultaneous presence of both nodal and tumoral pCR.

Molecular subtypes were classified into four categories based on receptor status: HR+/HER2− (including luminal A and luminal B HER2−), HR+/HER2+ (luminal B HER2+), HR−/HER2+ (HER2-enriched), and HR−/HER2− (triple-negative).

Continuous variables were presented as mean and standard deviation or median and interquartile range (IQR), depending on normal distribution. Categorical variables were presented as absolute values and frequencies.

Nodal pCR rates among molecular subgroups were compared using the chi-squared test (for categorical variables). A logistic regression model, including both univariate and multivariate analyses (enter method), was used to identify potential factors associated with nodal pCR.

A *p*-value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using IBM® SPSS® Statistics, version 25.

RESULTS

Four thousand four hundred and thirty-one surgeries were recorded from the Breast Surgery Unit's database, during the 5-year period between January 1st 2017 and December 31st 2021. Of these, 573 were performed in the context of a primary invasive node-positive breast cancer, treated with NAC, followed by ALND. After exclusions, 414 subjects were included in the analysis. The patient selection flowchart is presented in Fig. 1.

The median age was 53 [44–62] years, and 99.5% of patients were female. The most common histologic subtype was ductal or non-special type (NST), accounting for 91.6%, with a minority being lobular (7.3%) or other subtypes. Regarding molecular subtypes, the most common was HR+/HER2– (57.0%), followed by HR–/HER2– (17.2%), HR+/HER2+ (15.9%), and HR–/HER2+ (9.9%). The majority were moderately differentiated (61.6%), and the median Ki67 was 40 [25–60]. Most tumors were classified as cT2 (60.2%), followed by cT3 (30.4%) and cT1 (9.4%).

Regarding axillary staging, cN1 was the most common (81.4%), while cN2 and cN3 were observed in 11.1% and 7.5% of cases, respectively. Post-NAC MRI was performed in 346 patients (83.6%), with tumoral and nodal iCR rates of 31.5% and 50.9%, respectively. Breast-conserving surgery (BCS) was performed in 40.6% of patients, while the remaining (59.4%) underwent mastectomy, with an immediate post-mastectomy reconstruction rate of 41.9%. The median number of dissected lymph nodes was 14 [11–18], with 84.8% of patients having ≥10 lymph nodes dissected.

Patient, tumor, and surgical characteristics are summarized in Table 1.

Table 1: Sample characteristics.

Patient, tumor and surgery characteristics		n = 414
Female sex, n (%)		412 (99.5)
Age at surgery in years, median [IQR]		53 [44-62]
Genetic risk, n (%)		48 (11.6)
Histologic subtype, n (%)	Ductal/NST Lobular Mucinous Micropapillary Medullary	379 (91.6) 30 (7.3) 3 (0.7) 1 (0.2) 1 (0.2)
Molecular subtype, n (%)	HR+/HER2- HR+/HER2+ HR-/HER2+ HR-/HER2-	236 (57.0) 66 (15.9) 41 (9.9) 71 (17.2)
Differentiation grade, n (%)	G1 G2 G3 Missing	12 (2.9) 255 (61.6) 137 (33.1) 10 (2.4)
Ki67 (%), median [IQR]		40 [25-60]
cT stage, n (%)	T1 T2 T3	39 (9.4) 249 (60.2) 126 (30.4)
cN stage, n (%)	N1 N2 N3	337 (81.4) 46 (11.1) 31 (7.5)
Post-NAC MRI realization rate, n (%)		346 (83.6)
iCR, n (%) – n 346	Tumoral Nodal	109 (31.5) 176 (50.9)
Breast surgery, n (%)	BCT Mastectomy	168 (40.6) 246 (59.4)
Post-mastectomy immediate reconstruction, n (%) – n 246		103 (41.9)
Lymph nodes dissected, median [IQR]		14 [11-18]
≥ 10 lymph nodes dissected, n (%)		351 (84.8)

BCT: breast-conserving surgery; iCR: imagiologic complete response; IQR: interquartile range; MRI: magnetic resonance imaging; NAC: neoadjuvant chemotherapy; NST: non-special type.

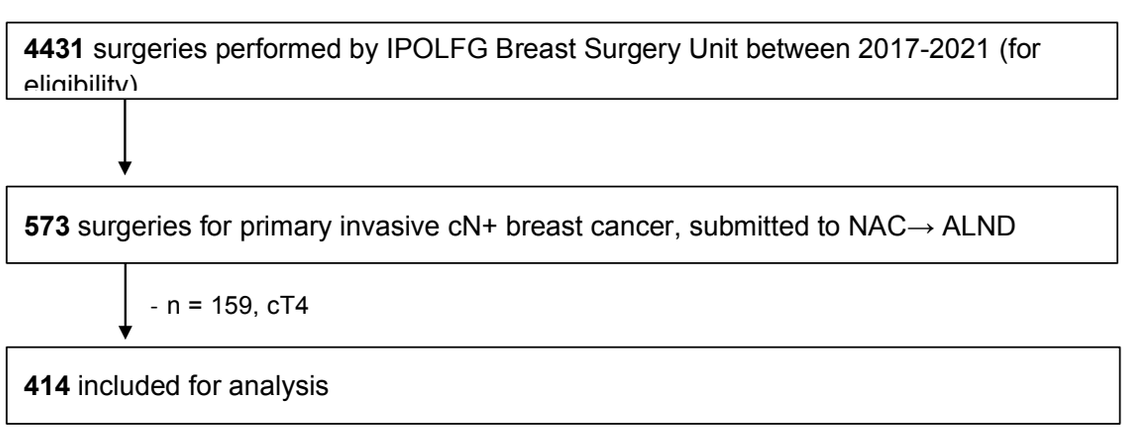

Figure 1: Study flowchart.

Overall, nodal pCR was 37.9% (141/414), while tumoral pCR was 29.9% (124/414). A total of 23.7% (98/414) of patients achieved simultaneous nodal and tumoral pCR.

The highest nodal pCR rates were observed in HR+/HER2+ (62.1%) and HR−/HER2+ (61.0%) tumors, followed by HR−/HER2− (56.3%), with the lowest rate in HR+/HER2− (21.6%) - p<0.001. When excluding cN3 tumors, the overall nodal pCR rate remained similar at 37.3% (143/383).

Nodal and tumoral pCR data are summarized in Table 2.

Table 2: Pathologic complete response (pCR), overall and by molecular subtype.

pCR	Overall	HR+/ HER2-	HR+/ HER2+	HR-/ HER2+	HR-/ HER2-	*p*-value
Tumoral, n (%)	124 (29.9)	31 (13.1)	30 (45.5)	22 (53.7)	41 (57.7)	<0.001
Nodal, n (%)	157 (37.9)	51 (21.6)	41 (62.1)	25 (61.0)	40 (56.3)	<0.001

pCR: pathologic complete response.

Among patients without nodal pCR, the median number of positive lymph nodes was 2.5.[1–5] When analyzed by molecular subtype, HR+/HER2− tumors had the highest median number of positive lymph nodes - 3 [1–6], p=0.038 (Table 3).

In the univariate analysis, the molecular subtypes HR+/HER2+ (OR 5.949, 95% CI 3.311–10.690, p<0.001), HR−/HER2+ (OR 5.668, 95% CI 2.815–11.412, p<0.001), and HR−/HER2− (OR 4.681, 95% CI 2.668–8.212, p<0.001) were associated with higher rates of nodal pCR (HR+/HER2- referent). Differentiation grade, specifically grade 3 (OR 5.512, 95% CI 3.337–8.142, p<0.001), was also positively associated with nodal pCR. The proliferative index Ki67 with a OR of 1.004 (95%CI 1.000-1.008) did not appear to relate with nodal pCR, neither histological subtype and cN staging.

Table 3: Positive lymph nodes in the absence of nodal pCR, overall and by molecular subtypes.

Positive lymph nodes			*p*-value
Overall, median [IQR]		2 [1-5]	
By molecular subtypes, median [IQR]	HR+/HER2- (n = 236)	3 [1-6]	0.038
	HR+/HER2+ (n = 66)	2 [1-3]	
	HR-/HER2+ (n = 41)	2 [1-5]	
	HR-/HER2- (n = 71)	2 [1-4]	

IQR: Interquartile range.

Variables with a statistically significant difference in the univariate analysis were included in the multivariate analysis. Here, the molecular subtypes HR+/HER2+ (OR 5.157, 95% CI 2.768–9.608, p<0.001), HR−/HER2+ (OR 4.207, 95% CI 1.935–9.147, p<0.001), and HR−/HER2− (OR 2.242, 95% CI 1.180–4.261, p=0.014) remained biological factors independently associated with nodal pCR, along with differentiation grade 3 (OR 4.075, 95% CI 2.448–6.784, p<0.001).

The logistic regression model is presented in Table 4.

Table 4: Logistic regression model.

	Univariate analyses OR [95%CI]	*p*-value	Multivariate analyses OR [95%CI]	*p*-value
Molecular subtypes		*<0.001*		*<0.001*
HR+/HER2-	Reference		Reference	
HR+/HER2+	**5.949** [3.311-10.690]	*<0.001*	**5.157** [2.768-9.608]	*<0.001*
HR-/HER2+	**5.668** [2.815-11.412]	*<0.001*	**4.207** [1.935-9.147]	*<0.001*
HR-/HER2-	**4.681** [2.668-8.212]	*<0.001*	**2.242** [1.180-4.261]	*0.014*
Histological subtype		0.245		
Ductal	Reference			
Lobular	0.475 [0.199-1.135]	0.094		
Others	1.041 [0.172-6.302]	0.966		
Grade				
G1/G2	Reference		Reference	
G3	**5.512** [3.337-8.142]	*<0.001*	**4.075** [2.448-6.784]	*<0.001*
Ki67 %	1.004 [1.000-1.008]	0.044		
cN stage		0.053		
N1	Reference			
N2	0.426 [0.205-0.888]	0.023		
N3	1.263 [0.602-2.648]	0.506		

CI: confidence interval; OR: odds-ratio.

DISCUSSION

NAC is an essential component of breast cancer treatment. Two of its main advantages are the potential for tumor cytoreduction and the insights it provides into tumor biology. It is expected that NAC response will be higher in tumors with certain intrinsic characteristics, such as Her2-positive and triple-negative (TN) molecular subtypes.[11,12] With this knowledge, we can optimize not only systemic treatment but also surgical approaches. In the breast, this has been reflected in a technical shift from mastectomy to breast-conserving surgery (BCS). However, in the axilla, this de-escalation strategy remains less well defined.

The sentinel lymph node biopsy (SLNB) approach in cN0 tumors after NAC is already well-established,[18,19] but for cN1 tumors that become ycN0, the role of SLNB remains uncertain. To achieve the acceptable false-negative rate (FNR) of ≤10%, strategies based on subgroup analyses from prospective studies have been developed, such as targeted axillary dissection (TAD), which involves excising the previously identified metastatic lymph node along with SLNB.[6-8] Since then, many techniques have been developed, and TAD is now included in international guidelines as a category 2B recommendation.[9,10]

However, there are some drawbacks to TAD[20]—it requires a multi-step procedure that can be difficult to implement in some hospital settings, is time- and cost-consuming, and involves significant variability in the methods used to reference and recover the clipped node during surgery[6] (guidewire, radioactive or magnetic seeds, infrared light, carbon particles), some of which are prohibited by national regulations. Additionally, it is challenging to determine the exact number of lymph nodes that need to be marked, and in up to 30% of cases, the clip may not be found in the operating field.[21,22] While morbidity could theoretically be similar to that of SLNB, long-term follow-up results are lacking.

In an effort to simplify this approach, we aimed to identify tumor intrinsic factors associated with nodal pCR, where axillary surgery could potentially be more conservative, such as using the standard SLNB technique.

In this study, comprised by a population of 414 patients treated with NAC in a high-volume, breast-dedicated unit with standardized treatment protocols, we found a nodal pCR rate similar to that reported in other published series.[12,23] Boughey *et al*[12] report an overall nodal pCR rate of 41.1%, while Montagna *et al*[23] report a rate of 46.0%. In the latter, a more contemporary series, nodal pCR is evaluated in SLNB specimens, as opposed to our study, where axillary staging is performed using ALND specimens, providing a more precise evaluation of nodal response. In fact, the median number of lymph nodes resected in ALND specimens is 14, with approximately 85% of patients having ≥10 lymph nodes excised.

We observed that the nodal response to NAC seems to differ among molecular subtypes, being higher in HR+/HER2+ (62.1%), HR−/HER2+ (61.0%), and HR−/HER2− (56.5%) tumors, and lower in HR+/HER2− tumors (21.6%) — $p<0.001$. This is consistent with the previously mentioned series—Bougey *et al*[12] reported nodal pCR rates of 64.7% in Her2+ tumors, 49.9% in triple-negative (TN) and just 21.1% in HR+/HER2− ($p<0.0001$) [12]; Montagna et al. [23] also reported similar distribution among molecular subtypes, but with higher pCR rates in Her2+ tumors (HR+/HER2+ 55%, HR−/HER2+ 78%), which may be explained by the use of dual Her2 blockade with trastuzumab and pertuzumab. Furthermore, in our series, among those without nodal pCR, the median number of positive lymph nodes was higher in HR+/HER2− tumors ($p=0.038$).

We conducted a logistic regression model to identify potential biological tumor characteristics associated with nodal pCR. In univariate analyses, molecular subtypes HR+/HER2+, HR−/HER2+, and HR−/HER2− were associated with higher rates of nodal pCR, as well as differentiation grade 3. In multivariate analysis, molecular subtypes HR+/HER2+ (OR 5.157, 95% CI 2.768–9.608, $p < 0.001$), HR−/HER2+ (OR 4.207, 95% CI 1.935–9.147, $p < 0.001$), and HR−/HER2− (OR 2.242, 95% CI 1.180–4.261, $p = 0.014$) remained independently associated with nodal pCR, along with grade 3 (OR 4.075, 95% CI 2.448–6.784, $p < 0.001$).

These data suggest that for Her2+ and TN tumors, and possibly those with differentiation grade 3, axillary surgery in ycN0 after NAC could be more conservative and simplified, such as the technique of SLNB alone.

Once again, this de-escalation based on molecular subtypes is corroborated by the preliminary results of the first prospective multicenter trial evaluating the "watch and wait" approach for selected breast cancers.[13] In this trial, omitting surgery in Her2 and TN tumors, cT1-2 and cN0-1, with pCR confirmed by vacuum-assisted core biopsy (VACB), did not result in ipsilateral recurrence, with a median follow-up of 26.4 months.

In contrast, in our study, nodal pCR in luminal tumors occurred in only about 1 in 5 patients, raising questions about whether the SLND plus clip strategy is sufficient. In our series of targeted axillary dissection (TAD) (data not shown – presented as oral communication at the Portuguese Society of Surgery Congress 2022), with 32 procedures performed since 2022, 31.3% (10) required a "second rescue" ALND, and 80.0% (8) of these cases occurred in HR+/HER2- tumors (p<0.05). All luminal A and about 2/3 of luminal B Her2- tumors submitted to TAD, required ALND.

Another important topic to corroborate our impression is the variability in the accuracy of predicting pCR between subtypes. In our center, the imaging response after NAC is assessed using mammary MRI. During the same 5-year period, we evaluated the accuracy of this imaging method in predicting tumoral and nodal pCR (data not shown – presented as oral communication at the 43rd European Surgical Oncology Congress, 2024[24]). The accuracy is generally better in the breast rather than in the axilla, with accuracy rates of 76.9% and 60.7%, respectively. In both cases, HR+/HER2- tumors have the lowest sensitivity and positive predictive value in predicting pCR, whereas TN and Her2+ tumors show more accurate imaging responses. Given this, is it reasonable, in luminal tumors, to rely solely on imaging response to define surgery? This data suggests that tumor biology, particularly molecular subtypes, should be taken into account.

One question remains—how many lymph nodes should be excised in SLNB? Two of the prospective randomized trials evaluating SLNB in cN1→ycN0 after NAC show a false-negative rate (FNR) of <10% when ≥3 lymph nodes are excised.[2,3] Another study shows the same result with ≥2 lymph nodes excised.[4] Although it has been shown that three or more SLNs are found in >90% of cases with dual-tracer mapping,[22] we agree with Classe *et al*[5] – the number of SLNs removed is variable and cannot be anticipated, and so the selection of patients who benefit from de-escalation of axillary surgery, should be based on tumor biology and independent from the number or lymph nodes removed.

To finish, a recent large retrospective single-institution study with 688 patients[1] aimed to compare the long-term results of SLNB after NAC in cN1/2 patients who turned into ycN0, compared to cN0 patients. After 10 years of follow-up, axillary recurrences occurred in 1.8% of patients in the cN1/2→ycN0 group and in 1.6% in the cN0 group. Distant recurrences were 16.6% *vs* 13.1%, respectively (p=0.148). Again, these results were independent of the number of SLNs retrieved, as there were no requirements for it. These data corroborate our hypothesis: SLNB is a valid option for ycN+→cN0 patients after NAC, with no worse outcomes, especially in tumors with a higher chance of nodal pCR—such as Her2, TN, and grade 3 tumors. In contrast, for luminal tumors (HR+/HER2-), SLNB alone for axillary staging may not be sufficient.

CONCLUSION

In this large series of 414 node-positive patients treated with NAC followed by ALND, the specimen that better represents the axilla, the overall nodal pCR rate was 37.9%. being higher in molecular subtypes that express Her2 and in TN tumors. In the regression model, these same subtypes, along with differentiation grade 3, were identified as independent factors positively associated with nodal pCR.

These results support the idea that axillary surgery after NAC should be tailored according to tumor biology. By recognizing which tumors are more likely to achieve nodal pCR, the so-called "good responders," we can determine which patients might be suitable candidates for a more simplified axillary approach after NAC, such as SLNB alone. In this series, HR+/HER2+, HR-/HER2+, HR-/HER2-, and possibly grade 3 tumors appear to be the most promising targets for this strategy.

ACKNOWLEDGMENTS

This study used data collected from patients treated at Instituto Português de Oncologia de Lisboa Francisco Gentil (IPOLFG). The reporting and interpretation of data are the sole responsibility of the authors.

PRIZES AND PREVIOUS PRESENTATIONS

Presented as a poster at *San Antonio Breast Cancer Symposium 2023,* and published as an Abstract: Gonçalves B, Costeira B, Cunha CF, Oom R, Costa C, Moniz JV, Abecasis N, Santos CR (2024). Abstract PO2-23-03: Potential Candidates for Conservative Axillary Surgery after Neoadjuvant Chemotherapy. *Cancer Res.* 84 (9_Supplement): PO2-23-03.

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 patient data.

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 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.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

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.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

CONTRIBUTORSHIP STATEMENT

BPG: Study concepts and design; data acquisition; data and statistical analysis, manuscript preparation, editing and review.
BC and MCG: Data acquisition; data and statistical analysis, manuscript editing and review.
RO: Study concepts and design; manuscript editing and review.
CSC, JVM and NA: Manuscript editing and review.
CRS: Study concepts and design; manuscript preparation, editing and review; supervision.
All authors approved the final version to be published.

DECLARAÇÃO DE CONTRIBUIÇÃO

BPG: Conceitos e desenho do estudo; aquisição de dados; análise estatística e dos dados, preparação, edição e revisão do manuscrito.
BC e MCG: Aquisição de dados; análise estatística e dos dados, edição e revisão do manuscrito.
RO: Conceitos e desenho do estudo; edição e revisão do manuscrito.
CSC, JVM e NA: Edição e revisão do manuscrito.
CRS: Conceitos e desenho do estudo; preparação, edição e revisão do manuscrito; supervisão.
Todos os autores aprovaram a versão final a ser publicada.

REFERENCES

1. Galimberti V, Ribeiro Fontana SK, Vicini E, Morigi C, Sargenti M, Corso G,et al. This house believes that: Sentinel node biopsy alone is better than TAD after NACT for cN+ patients. Breast. 2023; 67: 21-25
2. 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; 310:1455-61.
3. 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;14:609-18.
4. Boileau JF, Poirier B, Basik M, Holloway CM, Gaboury L, Sideris L,et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol. 2015;33:258-64.

5. Classe JM, Loaec C, Gimbergues P, Alran S, de Lara CT, Dupre PF, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Res Treat. 2019;173:343-52.
6. Gante I, Maldonado JP, Figueiredo Dias M. Marking Techniques for Targeted Axillary Dissection Among Patients With Node-Positive Breast Cancer Treated With Neoadjuvant Chemotherapy. Breast Can cer.2023;17:11782234231176159.
7. Boughey JC, Ballman KV, Le-Petross HT, McCall LM, Mittendorf EA, Ahrendt GM,et al. Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting With Node-positive Breast Cancer (T0-T4, N1-N2) Who Receive Neoadjuvant Chemotherapy: Results From ACOSOG Z1071 (Alliance). Ann Surg. 2016;263:802-7.
8. Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ,et al. Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. J Clin Oncol. 2016;34:1072-8.
9. Loibl S, André F, Bachelot T, Barrios CH, Bergh J, Burstein HJ, et al. Electronic address: clinicalguidelines@esmo.org. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2024;35:159-82. doi: 10.1016/j. annonc.2023.11.016.
10. National Comprehensive Cancer Network® (NCCN®) Guidelines Version 1.2025 - Breast Cancer. [Accessed February 2025]. Available at: https://www.nccn.org/guidelines/guidelines-detail?id=1419.
11. Mamtani A, Barrio AV, King TA, Van Zee KJ, Plitas G, Pilewskie M,et al. How Often Does Neoadjuvant Chemotherapy Avoid Axillary Dissection in Patients With Histologically Confirmed Nodal Metastases? Results of a Prospective Study. Ann Surg Oncol. 2016;23:3467-74.
12. Boughey JC, McCall LM, Ballman KV, Mittendorf EA, Ahrendt GM, Wilke LG,et al. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer: findings from the ACOSOG Z1071 (Alliance) Prospective Multicenter Clinical Trial. Ann Surg. 2014;260:608-14; discussion 614-6.
13. Kuerer HM, Smith BD, Krishnamurthy S, Yang WT, Valero V, Shen Y,et al. Eliminating breast surgery for invasive breast cancer in exceptional responders to neoadjuvant systemic therapy: a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2022;23:1517-24.
14. Samiei S, Simons JM, Engelen SM, Beets-Tan RG, Classe JM, Smidt ML, et al. Axillary pathologic complete response after neoadjuvant systemic therapy by breast cancer subtype in patients with initially clinically node-positive disease: a systematic review and meta-analysis. JAMA Surg. 2021;156:e210891.
15. Choi HJ, Ryu JM, Kim I, Nam SJ, Kim SW, Yu J,et al. Prediction of axillary pathologic response with breast pathologic complete response after neoadjuvant chemotherapy. Breast Cancer Res Treat. 2019;176:591-6.
16. Kantor O, Sipsy LM, Yao K, James TA. A Predictive Model for Axillary Node Pathologic Complete Response after Neoadjuvant Chemotherapy for Breast Cancer. Ann Surg Oncol. 2018;25:1304-11.
17. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK,et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67:93-9.
18. Hunt KK, Yi M, Mittendorf EA, Guerrero C, Babiera GV, Bedrosian I, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. Ann Surg. 2009;250:558-66.
19. Pilewskie M, Morrow M. Axillary nodal management following neoadjuvant chemotherapy: a review. JAMA Oncol. 2017;3:549-55.
20. Ferrarazzo G, Nieri A, Firpo E, Rattaro A, Mignone A, Guasone F, et al. The role of sentinel lymph node biopsy in breast cancer patients who become clinically node-negative following neo-adjuvant chemotherapy: a literature review. Curr Oncol.2023; 30:8703-19.
21. Hartmann S, Reimer T, Gerber B, Stubert J, Stengel B, Stachs A. Wire localization of clip-marked axillary lymph nodes in breast cancer patients treated with primary systemic therapy. Eur J Surg Oncol. 2018;44:1307-11.
22. Nguyen TT, Hieken TJ, Glazebrook KN, Boughey JC (2017). Localizing the Clipped Node in Patients with Node-Positive Breast Cancer Treated with Neoadjuvant Chemotherapy: Early Learning Experience and Challenges. Ann Surg Oncol. 2017; 24:3011-6.
23. Montagna G, Mamtani A, Knezevic A, Brogi E, Barrio AV, Morrow M. Selecting Node-Positive Patients for Axillary Downstaging with Neoadjuvant Chemotherapy. Ann Surg Oncol. 2020;27:4515-22.
24. Gonçalves B, Costeira B, Machado M, Cunha CF, Oom R, Costa CS,et al. MRI validity in predicting breast cancer pathologic response after neoadjuvant chemotherapy. Eur J Surg Oncol. 2024;50:109303.