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SHORT COMMUNICATION

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Breast cancer subtypes affect the nodal response after neoadjuvant chemotherapy in locally advanced breast cancer: Are we ready to endorse axillary conservation?

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Abstract

We evaluated the impact of breast cancer subtypes on pathologic complete response (pCR) in 181 patients with positive nodes undergoing neoadjuvant chemotherapy (NAC). After NAC, patients underwent surgery, with sentinel lymph node biopsy (SLNB) or axillary dissection (ALND). In 28.2% of cases a pCR was achieved, with the highest rate in Her2+ and triple negative tumors. Overall, nodal pCR was more frequent than breast pCR ($P = 0.003$) with higher percentages in Her2+ and LLB-Her2+ ($P < 0.05$). In the Her2+ group, nodal pCR was observed only with breast pCR. Thus, in Her2+ tumors, breast pCR predicts node pCR, supporting the use of SLNB in this subgroup to stage the axilla avoiding ALND.

KEYWORDS

axillary surgery, breast cancer, lymph node surgery, neoadjuvant chemotherapy, pathologic complete response, tumour subtype

1 | INTRODUCTION

Neoadjuvant chemotherapy (NAC) is increasingly used as the standard treatment modality for locally advanced breast cancer (BC). In addition to reducing tumor size, NAC can eradicate metastases in the regional lymph nodes. According to literature, pathologic complete response (pCR) rates have improved, occurring in 33%-37% of cases in the breast and in 20%-61% in the nodes, with variation based on tumor subtypes. While the achievement of breast pCR improves the rate of breast-conserving surgery, it has been suggested that nodal pCR could reduce the need for axillary dissection (ALND) in pre-NACT clinically node-positive patients, particularly in HER2+ disease.[1,2]

The aim of this study was to evaluate the impact of the immunohistochemical BC subtypes on breast and nodal pCR rates in patients with clinically nodal positive (cN+) disease at presentation.

2 | MATERIAL AND METHODS

The study was approved by the Institutional Review Boards. We identified 181 consecutive patients with cN+ BC, confirmed by cytology or biopsy and without distant metastases. Between January 2011 and January 2017 patients received NAC (4 cycles of doxorubicin plus cyclophosphamide every 2 or 3 weeks, then 12 cycles of

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paclitaxel weekly or 4 cycles of paclitaxel/docetaxel every 2 or 3 weeks, with the addition of trastuzumab in HER2+ cases). The stage of disease before and after NAC was assessed by clinical and radiologic examination. Based on the immunohistochemical features on biopsies, tumors were classified as luminal A-like (LLA), luminal B-like Her2 negative (LLB), Luminal B-like Her2 positive (LLB-Her2+), Her2 positive (non luminal: Her2+), and triple negative (TN) according to the 2013 St. Gallen Consensus Conference.[3]

All suspicious-appearing axillary lymph nodes according to standard ultrasonographic features were confirmed by cytology or biopsy, without nodal clip placement.

After NAC, all patients underwent breast surgery (mastectomy or breast conserving). Nodal surgery consisted either of ALND (range 6-24 nodes) or sentinel lymph node biopsy (SLNB) with preoperative lymphoscintigraphy and excision of 3-5 nodes to reduce the false negative rate.[4] The decision between SLNB and ALND relied on the response to therapy, the extent of the tumor before and after therapy and the tumor subtype. Each case was discussed in the weekly multidisciplinary meeting and the 2 options were shared with patients. When indicated, patients underwent appropriate radiation therapy.

Specimens were examined according to standardized protocols.[5] SLNs were entirely submitted for histology, including immunohistochemical confirmation of metastases. Evidence of nodal response to NAC, such as the presence of areas of scarring, sometimes with macrophage aggregates, was reported. Pathologic response was graded according to the MD Anderson residual cancer burden calculator[6] and classified according to the 7th edition of the AJCC staging system.[7] Breast and nodal pCR were classified as ypT0/ypTis and ypN0(i-) respectively.

2.1 | Statistical analysis

Quantitative variables were described as mean and range, while qualitative variables as number and percentage. Differences in the rate of ypT0/ypTis and ypN0(i-), both overall and in each tumor subtype, were evaluated using the χ^2 test.

To determine factors associated with pCR after NAC, univariate and multivariable logistic regression models were used. Results of both univariate and multivariate analysis were expressed in hazard ratios and 95% CIs. Statistical significance was set at $P < 0.05$. Analyses were performed using IBM SPSS Statistics for Window Version 23.0 (Armonk, NY) and GraphPad Prism (GraphPad, Inc, San Diego, CA).

3 | RESULTS

Patients and tumor characteristics are summarized in Table 1. By selection criteria all patients had nodal disease. The most common histologic subtype was ductal carcinoma and the majority of the tumors (59.1%) were of high nuclear grade (G3). Luminal A-like

TABLE 1 Clinico-pathological features of the study population

Characteristics	Total n = 181	LLA 9.9%	LLB 35.9%	LLB-Her2+ 16.6%	Her2+ 20.4%	TN 17.1%
Age, y						
<50	43.6%	50%	46.3%	40%	37.8%	45.2%
50+	56.4%	50%	53.8%	60%	62.2%	54.8
cT						
cT1	11.6%	0	12.3%	16.7%	10.8%	12.9%
cT2	65.2%	72.2%	63.1%	70%	62.2%	64.5%
cT3	16%	16.7%	13.8%	10%	27%	12.9%
cT4	7.2%	11.1%	10.8%	3.3%	0	9.7%
cN						
cN1	51.4%	63.2%	46.9%	50%	45.9%	61.3%
cN2	29.3%	21.1%	32.8%	26.7%	29.7%	29%
cN3	19.3%	15.8%	20.3%	23.3%	24.3%	9.7%
Histotype						
Ductal	93.9%	83.3%	89.2%	96.7%	100%	100%
Lobular	6.1%	16.7%	10.8%	3.3%	0	0
Nuclear grading						
G1	13.8%	27.8%	30.8%	0	0	0
G2	27.1%	61.1%	27.7%	30.0%	16.2%	16.1%
G3	59.1%	11.1%	41.5%	70%	83.8%	83.9%
Pathologic response						
Complete	28.2%	0	21.5%	20%	59.5%	29%
Incomplete	70.7%	100%	78.5%	80%	40.5%	71%

Her2+, Her2 positive; LLA, luminal A-like; LLB, luminal B-like; LLB-Her2+, luminal B-like Her2 positive; TN, triple negative.

tumors represented 9.9% of cases (18 pts), LLB 35.9% (65 pts), LLB-Her2+ 16.6% (30 pts) Her2+ 20.4% (37 pts), and TN 17.1% (31 pts). After NAC, 66 patients (36.5%) received breast conserving surgery. Ninety (50%) were treated with ALND, 55 (30.4%) with SLNB only and 36 (28.6%) were converted from SLNB to ALND. Representative pictures of post-NAC lymph nodes are provided in Figure 1.

Pathologic complete response in both breast and axilla was achieved in 51/181 patients (28.2%). pCR was more frequent in nodes than in breast (45.9% vs 30.9% respectively; $P = 0.003$). There was no significant difference between clinical nodal stage (cN1-3) and frequency of nodal pCR, except for the LLB subtype, in which cN1 was significantly correlated with higher nodal pCR rate ($P = 0.001$).

The rate of pCR differed according to the tumor subtype. In the Her2+ group breast pCR was achieved in 59.5% of cases, while nodal pCR was observed in 81% of patients ($P = 0.04$). In this group, every time a breast pCR was achieved, this was associated with nodal pCR. LLB-Her2+ showed a pCR in 6/30 cases (20%), again with a significantly higher percentage of nodal than breast pCR ($P = 0.03$). Within TN and LLB, pCR was achieved in 9/31 (29%) and 14/65 (21.5%) cases respectively, with no difference between breast and axillary response rate. In these three subtypes, the breast pCR in each single patient was not invariably associated with nodal pCR. Finally, there were no pCR in the LLA subtype (Table 2).

On univariate analysis, only immunohistochemical subtypes and nuclear grade significantly correlated with pCR ($P = 0.01$) On multivariate analysis age, clinical stage, and grading were not significantly associated with pCR; receptor subtype remained the only significant predictor of pCR ($P = 0.02$) (Table 3).

4 | DISCUSSION

We confirm a correlation between BC subtypes and axillary pCR in a consecutive series of cN+ patients who received NAC and surgery at our Institutions. Overall pCR was achieved in almost one third of patients, in line with recent reports.[2] Luminal A tumors never achieved a pCR. The pCR rate was higher in patients with non-luminal Her2+ and TN BC.[8] High nuclear grade was positively correlated with overall response rate. In all tumor subtypes the percentage of pCR was significantly higher in nodes. The difference between nodal and breast response was significant only in Her2+ and LLB-Her2+ tumors ($P = 0.04$ and 0.03 respectively). Intriguingly, in the Her2+

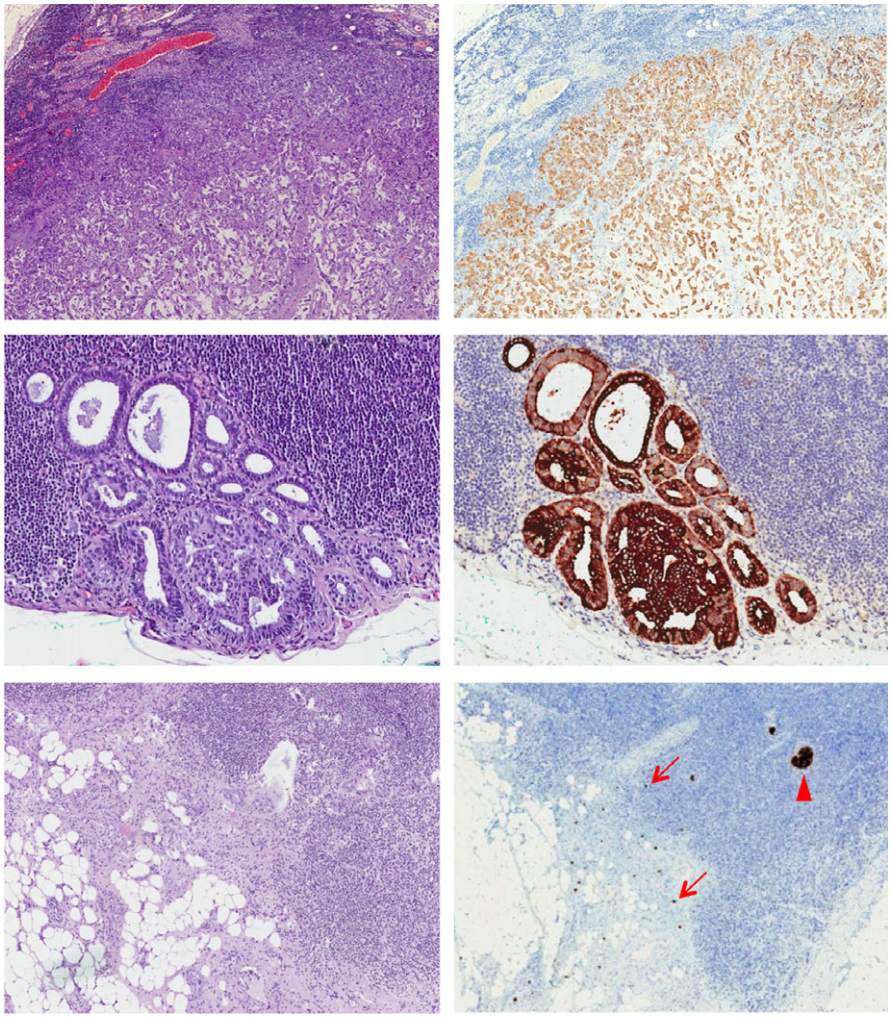

FIGURE 1 Post-NAC lymph nodes. Macro- and micrometastases (A-C), immunostained with pancitokeratin (B-D). Subcapsular fibrosis consistent with the effect of NAC (E). Residual tumor cells, immunostained with pancitokeratin (F) (arrows). NAC, neoadjuvant chemotherapy [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Relation between immunohistochemical subtype and pathologic complete response rate

	pCR rate 28.2%	ypT0/is 30.9%	ypN0(i-) 45.9%	*P* value	OR (95%CI)
LLA	0	5.6%	11.1%	0.55	0.47 (0.03-5.71)
LLB	21.5%	23.1%	35.4%	0.12	0.55 (0.25-1.18)
LLB-Her2+	20%	23.3%	50%	0.03*	0.3 (0.1-0.92)
Her2+	59.5%	59.5%	81.1%	0.04*	0.34 (0.12-0.98)
TN	29%	35.5%	41.9%	0.6	0.76 (0.27-2.12)

*Statistically significant values.
Her2+, Her2 positive; LLA, luminal A-like; LLB, luminal B-like; LLB-Her2+, luminal B-like Her2 positive; OR, odds ratio; TN, triple negative.

group a nodal pCR was observed only in presence of breast pCR. Our observation that in Her2+ tumors breast pCR predicts the negative nodal status support the hypothesis that in patients with pre-NAC cN+, in case of documented breast pCR and downstaging on axilla, SLNB may be used to efficiently stage the axilla avoiding ALND.

Regardless of the rate of breast response, we observed the highest nodal pCR in Her2+ and LLB-Her2+ tumors. One possible explanation could be related to the enhancement of tumor cell killing by the innate and adaptive immune system activation, which has been demonstrated in experimental models of Her2+ tumors.[9] These mechanisms would be more efficient within the lymphoid tissue of metastatic nodes.

According to the literature, NAC is effective in achieving pCR in cN+ patients, and nodal pCR is associated with better overall survival and recurrence-free survival.[10] Based on these data, SLNB has been proposed for patients with cN+ and clinical node downstaging after NAC.[11] However, the optimal surgical management of the axilla in this setting is still controversial, for several reasons. One important issue is the need for the correct identification of nodal pCR by imaging.[12] Moreover, the reported false negative rate on pathologic examination of SLNB has been reported as higher in NAC than in the adjuvant setting, probably due to modifications of the breast lymphatic drainage secondary to the node metastatic deposits or, perhaps, to the effects of the systemic therapy. For this reason, the placement of a clip in the biopsy/cytology proven metastatic lymph node before NAC or the use of dual mapping to facilitate the SLN identification were proposed, with encouraging results.[13] Importantly, the results of the SENTINA protocol show that the accuracy of SLNB is proportional to the number of lymph nodes removed, with a false negative rate consistently below 10% when three or more sentinel lymph nodes are resected.[4]

An important issue is the influence of tumor biology on pCR. Receptor subtype, as assessed by immunohistochemistry on pre-NAC biopsies, can predict the response of BC to NAC.[2] In our series, the overall pCR rate was significantly correlated only with receptor subtype and nuclear grading of the tumors ($P = 0.01$). On multivariate analysis, receptor subtype remained the only significant predictor of overall pCR ($P = 0.02$). In line with recent reports[2] the highest pCR rates in our series were achieved in Her2+ and TN tumors (59.5% and 29% respectively). In light of the impact of tumor subtype on the achievement of pCR, the need for breast surgery is being questioned in Her2+ and TN tumors, when a post NAC biopsy indicates a breast pCR,[14] and clinical trials are currently ongoing, in which breast surgery is omitted in patients with these tumor subtypes and documented breast pCR.[15] However, the optimal management of the axilla in this setting is still unknown. According to our

TABLE 3 Univariate and multivariate analysis of factors associated with pCR after NAC

		%	*P* value	OR (95% CI)	*P Value*	OR (95% CI)
Age	<50	27.8%	0.64	1 (0.97-1.03)	0.93	1 (0.97-1.03)
	50+	28.4%				
cT	cT1	42.9%	0.3	1.28 (0.8-2.04)	0.47	1.19 (0.73-1.94)
	cT2	24.6%				
	cT3	34.5%				
	cT4	15.4%				
cN	cN1	29%	0.57	1.13 (0.74-1.72)	0.44	1.19 (0.76-1.85)
	cN2	28.3%				
	cN3	25.7%				
Nuclear grading	G1	20%	0.01**	0.52 (0.31-0.88)	0.77	0.72 (0.39-1.3)
	G2	14.3%				
	G3	36.5%				
Subtype	LLA	0	0.01**	0.65 (0.5-0.85)	0.02**	0.69 (0.52-0.94)
	LLB	21.5%				
	LLB-Her2+	20%				
	Her2+	59.5%				
	TN	29%				

**Statistically significant values.
Her2+, Her2 positive; LLA, luminal A-like; LLB, luminal B-like; LLB-Her2+, luminal B-like Her2 positive; OR, odds ratio; TN, triple negative.

results, we conclude that in Her2+ tumors breast pCR predicts nodal pCR, favoring the use of SLNB in patients with pre-NAC cN+ in case of breast pCR and axillary downstaging.

The main limitation of this study resides in the lack of dual mapping or node clipping. However, at least 3 lymph nodes were obtained for each SLNB procedure. According to the results of the SENTINA trial the false negative rate is consistently less than 10% when at least 3 SLN are removed. Moreover, in our study the majority of patients (69.6%) underwent ALND, and all the lymph nodes were evaluated. Finally, we demonstrated areas of scarring in all SLN, consistent with the effect of NAC on the metastatic deposits.

CONFLICT OF INTEREST

None.

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