Is it Possible to Avoid Sentinel Lymph Node Biopsy in Breast Cancer Patients with a Positive Axillary Lymph Node with Pathologic Complete Response to Neoadjuvant Chemotherapy?

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É Possível Evitar a Biópsia do Linfonodo Sentinela em Pacientes com Câncer de Mama e Linfonodo Axilar Positivo com Resposta Patológica Completa à Quimioterapia Neoadjuvante?

¿Es Posible Evitar la Biopsia del Ganglio Centinela en Pacientes con Cáncer de Mama y Ganglio Axilar Positivo con Respuesta Patológica Completa a la Quimioterapia Neoadyuvante?

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ABSTRACT

Introduction: Breast cancer represents 24.5% of new cases of cancer in women worldwide. Neoadjuvant chemotherapy is an important tool in the treatment of this pathology, allowing less aggressive surgeries at the breast and axilla, minimizing sequelae. **Objective:** Analyze the possibility of avoiding sentinel lymph node biopsy in patients with breast cancer who have undergone neoadjuvant chemotherapy and who present complete pathological response at the primary tumor and axilla, treated at a reference institution in Brazil's Northeast. **Method:** Prospective, observational, cohort study in patients with breast cancer, undergoing neoadjuvant chemotherapy and operated at the *Hospital Haroldo Juaçaba*, from March 2019 to July 2021. **Results:** Forty-five female patients were enrolled in the study, with a mean age of 52.6 years. After neoadjuvant chemotherapy, nine patients (21.4%) had complete pathologic response at the breast and 17 (40.5%), complete pathologic response at the lymph nodes. Patients with complete response at the breast had a prevalence of complete response at lymph node 20.44 times higher than patients who did not have the same response. **Conclusion:** The complete pathologic response to neoadjuvant chemotherapy at the breast shows a tendency to predict the pathologic response at the axillary lymph nodes, raising the doubt that, with this condition, sentinel lymph node biopsy could be avoided without causing harm to the local control of breast cancer.
Key words: breast neoplasms; sentinel lymph node biopsy; neoadjuvant therapy.

RESUMO

Introdução: O câncer de mama representa 24,5% dos novos casos de neoplasias em mulheres no mundo. A quimioterapia neoadjuvante é uma importante ferramenta no tratamento dessa patologia, possibilita cirurgias menos agressivas na mama e axila, além de minimizar sequelas. **Objetivo:** Analisar a possibilidade de se evitar a realização da biópsia do linfonodo sentinela em pacientes com câncer de mama submetidas à quimioterapia neoadjuvante que apresentem resposta patológica completa no tumor primário e na axila, tratadas em uma instituição de referência no Nordeste brasileiro. **Método:** Estudo prospectivo, observacional, de coorte em pacientes com câncer de mama submetidas à quimioterapia neoadjuvante e operadas no Hospital Haroldo Juaçaba, no período de março de 2019 a julho de 2021. **Resultados:** Foram incluídas no estudo 45 pacientes, com média de idade de 52,6 anos, sendo todas do sexo feminino. Após quimioterapia neoadjuvante, nove pacientes (21,4%) apresentaram resposta patológica completa na mama e 17 (40,5%), resposta patológica completa nos linfonodos. Os pacientes com resposta completa na mama apresentaram uma prevalência de resposta completa em linfonodo 20,44 vezes superior aos pacientes que não tiveram a mesma resposta. **Conclusão:** A resposta patológica completa na mama à quimioterapia neoadjuvante mostra uma tendência em predizer uma resposta patológica nos linfonodos axilares, reforçando que, com essa condição, a biópsia do linfonodo sentinela poderia ser evitada sem causar prejuízos ao controle local do câncer de mama.
Palavras-chave: neoplasias da mama; biópsia de linfonodo sentinela; terapia neoadjuvante.

RESUMEN

Introducción: El cáncer de mama representa el 24,5% de los nuevos casos de neoplasias en mujeres de todo el mundo. La quimioterapia neoadyuvante es una herramienta importante en el tratamiento de esta patología, permitiendo cirugías menos agresivas en la mama y la axila, minimizando las secuelas. **Objetivo:** Analizar la posibilidad de evitar la biopsia del ganglio centinela en pacientes con cáncer de mama, sometidas a quimioterapia neoadyuvante, con respuesta patológica completa en el tumor primario y en la axila, tratadas en una institución de referencia del noreste de Brasil. **Método:** Estudio prospectivo, observacional, de cohorte en pacientes con cáncer de mama, sometidas a quimioterapia neoadyuvante y operadas en el *Hospital Haroldo Juaçaba*, en el período de marzo de 2019 a julio de 2021. **Resultados:** Se incluyeron 45 pacientes en el estudio, con una edad media de 52,6 años, y todos eran mujeres. Tras la quimioterapia neoadyuvante, nueve pacientes (21,4%) mostraron respuesta patológica completa en la mama y 17 (40,5%), respuesta patológica completa en los ganglios linfáticos. Las pacientes con respuesta completa en la mama presentaron una prevalencia de respuesta completa en el ganglio linfático 20,44 veces mayor que las pacientes que no tuvieron la misma respuesta. **Conclusión:** La respuesta patológica completa en la mama a la quimioterapia neoadyuvante muestra una tendencia a predecir una respuesta patológica en los ganglios linfáticos axilares, reforzando que, con esta condición, la biopsia del ganglio linfático centinela podría evitarse sin causar daño al control local del cáncer de mama.
Palabras clave: neoplasias de la mama; biopsia del ganglio linfático centinela; terapia neoadyuvante.

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INTRODUCTION

With approximately 2.3 million new cases estimated for 2020, breast cancer accounts for 24.5% of new cases of cancer in women, being the main cause of death related to female neoplasms, with 684,996 deaths expected for 2021, a total of 15.5% of deaths by cancer in women worldwide[1].

In Brazil, 73,610 new cases of breast cancer have been estimated for 2023, an incidence of 41.89 cases per 100 thousand women[1]. Deaths by breast cancer are ranked first of proportional mortality by cancer, corresponding to 16.5% of the total of deaths in 2022.

Neoadjuvant chemotherapy (NACT), initially indicated to treat locally advanced breast cancer, became a treatment option for operable breast cancer since 1990. There are no differences[2-4] regarding global survival (GS) while comparing adjuvant with neoadjuvant chemotherapy. However, the neoadjuvant treatment may possibly reduce the tumor volume and axillary compromise (downstaging), increasing the possibility of conserving surgery without affecting survival, being the Pathological Complete Response (pCR) an excellent predictor of the prognosis[5,6].

The Sentinel Lymph Node Biopsy (SLNB) was an important tool described in 1994 for axillary management of patients with breast cancer[7]. The axillary lymph node status is determinant to treat breast cancer and is a strong prognostic factor[7,8]. Randomized studies showed that SLNB reflects trustworthily the presence or absence of axillary metastases, with local control, disease-free survival (DFS) and GS similar to axillary emptying in patients with clinically negative axilla[9,10].

The studies ACOSOG Z1071[11] and AMAROS[12] went beyond the conserving of the axilla to avoid the mutilation caused by the dissection as an undisputed sentence for compromised metastatic lymph node. Both studies showed similar results for locoregional control and global survival when compared SLNB associated with radiotherapy *versus* axillary lymph node dissection in selected settings and patients with proven axillary metastasis[11-13].

For many years, the neoadjuvant post-chemotherapy standard-of-care was axillary lymph node dissection[14]. However, Fisher et al.[15] noticed that nearly 40% of the patients with positive axillary lymph node presented pCR post NACT and the rates were higher than 70% with the use of the anti-human epidermal growth factor receptor 2 (HER2).

The study ACOSOG Z1071[11] showed that SLNB was possible in initially positive axilla (cN1) which became negative after NACT. With acceptable false-positive rate utilizing dual-dyer and radioisotope marker and resecting three or more sentinel lymph nodes (ycN0), the procedure could be utilized with acceptable oncologic safety[11,13].

Some authors[16,17] reported that marking the suspected lymph node with metallic clip or iodine 123 in pre-treatment during ultrasound-guided biopsy the rate of false-negative became more acceptable which eventually made post-NACT reliable.

Recent analyzes showed that survival rate is more influenced by pCR than by the initial clinical status even in patients with pre-treatment axillary metastasis, strengthening the use of post-NACT sentinel lymph node biopsy[18].

The present study attempted to correlate the response of the primary breast tumor with lymph node metastasis post-NACT in women treated at a reference institution of the Brazilian Northeast region. The objective is to respond to the research question: "Is it possible to avoid SLNB in breast cancer patients with pathological complete response post-NACT?"

METHOD

Observational, prospective study conducted at "*Hospital Haroldo Juaçaba*", a reference of oncologic treatment in the North and Northeast regions from March 2019 to July 2021.

The population consisted in 45 women with breast cancer initially untreated with clinically positive axilla submitted to NACT and surgical treatment. The sample is non-probabilistic by convenience and formed by all the patients with breast cancer who met the inclusion criteria described below. The variables investigated were: immunohistochemical profile of the tumor, initial clinically positive cytology of lymph node, response to NACT in the breast and lymph nodes, including the objective response considered as addition to complete and partial response, positive sentinel lymph node, pre and post clinical staging chemotherapy, coincidence or not of the clinically pre-chemotherapy positive lymph node clipped with the sentinel lymph node resected during the surgery.

The inclusion criteria were 18-75 years old women diagnosed with larger than 2 cm breast invasive carcinoma, clinically positive axilla, clinical staging T2-T3 and N1-N2 who initiated NACT followed up at the Mastology of "*Hospital Haroldo Juaçaba*" who accepted to join the study after signing the Informed Consent Form.

Patients with metastases (M1) at diagnosis, submitted to excisional biopsy and previous axillary surgeries and normal axillary ultrasound were excluded.

Ultrasound-guided aspiration puncture with local anesthetic (xylocaine 4%) with placement of metal clip on clinically suspected palpable axillary lymph node was

performed and cytologic analysis with investigation of neoplastic cells before NACT. The patients were followed up periodically during chemotherapy with clinical analysis of the tumor response to the treatment.

After the conclusion of NACT, the patients were submitted to radical or conserving surgical procedure of breast and axilla based in clinical information with axillary approach and anatomopathology of the piece producing more accurate data about the response of the disease to the chemotherapy treatment.

To validate the reliability of NACT, the dual-tracer method was utilized to identify sentinel lymph nodes with intradermal injection of 0.8 mL technetium-99 sodium phytate, dose of 29.6 MBq (0.8 mCi) and 0.5 of patent blue, periareolar in the four cardinal points of the affected breast. The sentinel lymph node was located with a gamma radiation probe and visual identification, removed and sent to the pathologist who sliced in 2mm longitudinal serial cuts along its longer axis, and submitted to histological exam to detect the presence of metal clip during the process.

The study complied with ethical guidelines of Resolution 466/12 of the National Health Council (CNS)[19], respecting the dignity and ensuring the protection of human beings during the participation in clinical trials. The individual and collective bioethics of each participant was considered, in addition to autonomy, no-harm, beneficence, justice and equity to ensure the rights and duties while the study was being conducted as oriented by the scientific community.

Upon approval by the Institutional Review Board (IRB) of "*Universidade Federal do Ceará, Pró-Reitoria de Pesquisa (CEP/UFC/Propesq)*" and by the IRB of "*Instituto do Câncer do Ceará (ICC), Hospital Haroldo Juaçaba*" report number 3,227,730 (CAAE (submission for ethical review): 09507218.4.0000.5054) the data were collected.

The information and data obtained from the patients' charts were utilized for scientific objectives alone and the anonymity was secured. The data were tabulated in a Microsoft Excel spreadsheet and exported to the software Statistical Package for the Social Sciences (SPSS) with confidence interval of 95% for the analyzes performed.

In addition, the data were expressed as absolute and relative frequency. The frequencies of complete and objective response to breast and lymph nodes NACT were associated with other clinical characteristics through Fisher's exact test and Pearson chi-square test.

RESULTS

The current sample consisted in 45 patients with breast cancer. The mean age was 52.6 ±12.5 years, ranging from 26 to 74 years with 30 patients (66.7%) older than 45 years. The most prevalent T staging was T3 (n=27; 60%) and the most predominant staging N was N1 (n=32; 71.1%). Immunosuppression for estrogen receptor was observed in 25 patients (55.6%), progesterone receptor in 24 (53.3%) and HER2 in eight (17.8%). The majority of the patients presented phenotype luminal B (n=22; 48.9%) and 17 patients (37.8%), triple-negative tumors. The most prevalent tumor grade was II (n=27; 67.5%); the tumor grade was not determined for five patients (11.11%) of the sample.

Limphovascular invasion was found in four patients (9.8%) and none of them presented perineural invasion; the anatomopathological analysis was unable to determine the presence or absence of limphovascular and perineural invasion in four patients of the total sample. Forty-two patients were submitted to SLNB, of which 38 (90.4%) presented clip placed at the sentinel lymph node. Three patients (6.6%) of the initial sample of 45 did not undergo SLNB, one of them (2.2%) lost follow-up and two of them (4.4%) presented progression of the systemic disease. All 45 patients who presented clinically positive axilla (N1 or N2) were submitted to fine needle aspiration puncture (FNAP) and to cytological analysis of the suspected axillary lymph node; 30 (66.6%) presented positive result of neoplastic cells investigation, ten (22.2%), absence of neoplastic cells and five (11.1%), unsatisfactory sample (Figure 1).

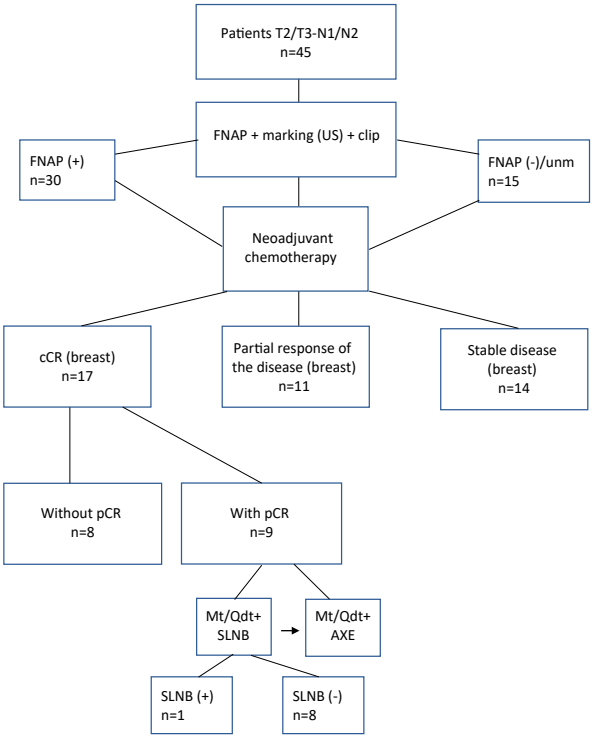

Figure 1. Flowchart of the study patients
Captions: FNAP = fine needle aspiration puncture; US = ultrasound; Unm = unsatisfactory material; cCR = clinical complete response; pCR = pathological complete response; Mt = mastectomy; Qdt = quadrantectomy; SLNB = sentinel lymph node biopsy; AXE = axillary emptying.

Most of the patients presented pathological partial response at the breast (n=19; 45.2%), followed by stable disease (n=14; 31.13%), and pCR (n=9; 21.4%). At clinical examination, NACT and pre-surgery, 17 patients presented clinical complete response (cCR), of which, as already mentioned, only nine presented correlation with pCR of the breast. None of the patients had disease progression at the breast. On lymph nodes, most of the patients presented pCR (n=17; 40.5%), followed by stable disease (n=13; 31.0%), disease progression (n=8; 17.8%) and partial pathological response (n=4; 9.5%). The rate of pCR was significantly higher on lymph node than on the breast (p = 0.001) (Table 1).

For triple-negative tumors, the majority of the pathological responses was stable disease (n=7; 43.8%) and pCR (n=7; 41.2%) in lymph nodes. However, no significant difference of the pathological response of the breast and lymph node was found for these patients (p = 0.188) (Table 1).

Patients with pCR of the breast presented rate in lymph node 20.44-fold higher (CI95%=2.23-187.69) than patients who had not pCR of the breast (p = 0.002) (Table 2).

Age (p = 0.161), staging T (p = 0.537) and N (p = 0.862), expression for estrogen receptor (p = 0.483), progesterone receptor (p = 0.591), phenotype (p = 0.588), tumor grade (p = 0.415) and presence of limphovascular invasion (p = 0.838) were not associated with pathological response of the breast. However, patients with positive HER2 presented pCR of the breast 12.50-fold higher (CI95%=2.13-73.47) than patients with negative HER2 (p = 0.006) (Table 3).

Regarding lymph nodes, age (p = 0.824), staging T (p = 0.542) and N (p = 0.921), expression for estrogen receptor (p = 0.408), progesterone receptor (p = 0.952), phenotype (p = 0.313), tumor grade (p = 0.189) and presence of limphovascular invasion (p = 0.531) were not associated with pathological response at the axilla. However, patients with positive HER2 had pCR in lymph node 36.43-fold higher (CI95%=1.90-697.60) than patients with negative HER2 (p < 0.001) (Table 3).

Table 2. Influence of the therapeutic response of primary tumor in the lymph node chain of women with breast cancer submitted to NACT

	CR breast		
	No	Yes	*p* value
CR lymph node			
No	24 (72.7%)*	1 (11.1%)	0.002
Yes	9 (27.3%)	8 (88.9%)*	

Captions: CR = complete response.
(*) p < 0.05, Fisher's exact test or Pearson's chi-square test.
Note: Absolute and percent frequency.

None of the variables investigated negatively influenced the rate of pCR of the breast, but for lymph nodes, regardless of age (p = 0.661), staging T (p = 0.262) and N (p = 0.327), expression of progesterone receptor (p = 0.204), of phenotype (p = 0.085), tumor grade (p = 0.056) and presence of limphovascular invasion (p = 0.823) with significant association with pathological response in lymph node, patients with positive HER2 presented objective pathological response in lymph node 17.73-fold higher (CI95%=1.03-334.50) than patients with negative HER2 (p = 0.011), and patients with negative ER presented objective pathological response in lymph node 4.36-fold higher (CI95%=1.16-16.32) than patients with positive ER (Table 4).

For triple-negative tumors, none of the variables investigated presented significant association with pCR or objective in breast or lymph nodes.

DISCUSSION

Surgical approach to breast cancer is being downsized, since the initial Halsted[20,2] radical mastectomy with total excision of the breast, chest muscles and axillary ganglionary chains and later with Patey and Dyson[22] chest muscles conserving surgery. Veronesi et al.[23] proposed the next step for breast conserving surgery. At the axilla, the rule was axillary ganglionary emptying until recently

Table 1. Profile of therapeutic response in primary tumor and lymph node chain of women with breast cancer or triple-negative breast cancer submitted to neoadjuvant chemotherapy

				Triple-negatives		
	Breast	Lymph node	*p* value	Breast	Lymph node	*p* value
Therapeutic response						
CR	9 (21.4%)	17 (40.5%)*	< 0.001	3 (18.8%)	7 (41.2%)	0.188
PR	19 (45.2%)*	4 (9.5%)		6 (37.5%)	4 (23.5%)	
SD	14 (31.1%)	13 (31.0%)		7 (43.8%)	4 (23.5%)	
DP	0 (0.0%)	8 (17.8%)		0 (0.0%)	2 (11.8%)	

Captions: CR = complete response; PR = partial response; SD = stable disease; DP = disease progression.
(*) p < 0.05, Fisher's exact test or Pearson's chi-square test.
Note: Data expressed as absolute and percent frequency.

Table 3. Indicators of complete therapeutic response of a primary tumor and lymph node chain of women with breast cancer submitted to NACT

	CR breast		*p* value	CR lymph node		*p* value
	No	Yes		No	Yes	
Age						
Up to 45 years	10 (30.3%)	5 (55.6%)	0.161	8 (32.0%)	6 (35.3%)	0.824
More than 45 years	23 (69.7%)	4 (44.4%)		17 (68.0%)	11 (64.7%)	
T						
T2	11 (33.3%)	4 (44.4%)	0.537	8 (32.0%)	7 (41.2%)	0.542
T3	22 (66.7%)	5 (55.6%)		17 (68.0%)	10 (58.8%)	
N						
N1	23 (69.7%)	6 (66.7%)	0.862	18 (72.0%)	12 (70.6%)	0.921
N2	10 (30.3%)	3 (33.3%)		7 (28.0%)	5 (29.4%)	
ER						
No	14 (42.4%)	5 (55.6%)	0.483	10 (40.0%)	9 (52.9%)	0.408
Yes	19 (57.6%)	4 (44.4%)		15 (60.0%)	8 (47.1%)	
PR						
No	15 (45.5%)	5 (55.6%)	0.591	12 (48.0%)	8 (47.1%)	0.952
Yes	18 (54.5%)	4 (44.4%)		13 (52.0%)	9 (52.9%)	
HER2						
No	30 (90.9%)*	4 (44.4%)	0.006	25 (100.0%)*	10 (58.8%)	<0.001
Yes	3 (9.1%)	5 (55.6%)*		0 (0.0%)	7 (41.2%)*	
Phenotype						
Luminal A	3 (9.1%)	0 (0.0%)	0.588	3 (12.0%)	0 (0.0%)	0.313
Luminal B	16 (48.5%)	5 (55.6%)		12 (48.0%)	9 (52.9%)	
HER2+	1 (3.0%)	1 (11.1%)		0 (0.0%)	1 (5.9%)	
Triple-negative	13 (39.4%)	3 (33.3%)		10 (40.0%)	7 (41.2%)	
Tumor grade						
I	4 (13.8%)	0 (0.0%)	0.415	4 (18.2%)	0 (0.0%)	0.189
II	19 (65.5%)	7 (87.5%)		13 (59.1%)	12 (80.0%)	
III	6 (20.7%)	1 (12.5%)		5 (22.7%)	3 (20.0%)	
LVI						
No	27 (90.0%)	7 (87.5%)	0.838	20 (87.0%)	14 (93.3%)	0.531
Yes	3 (10.0%)	1 (12.5%)		3 (13.0%)	1 (6.7%)	

Captions: CR = complete response; T = tumor size; N = lymph node; ER = estrogen receptor; PR = progesterone receptor: HER2 = human epidermal growth factor receptor 2; LVI = limphovascular invasion.
(*) $p < 0.05$ = Fisher's exact test or Pearson's chi-square test.
Note: Data expressed in absolute and percent frequency.

Giuliano et al.[7] reported the feasibility of SLNB, although less invasive, but able to cause sequealae[24].

Metastatic axillary lymph node is one of the main prognosis of breast cancer according to the analysis of sentinel lymph node or axillary emptying. Both procedures, even in different proportions, can cause adverse effects as lymphedema, bruises, seroma and infections[9,22,25].

The profile of treatment is changing with the raising use of NACT and new information about the disease have been appearing. Recent studies showed that the survival rate is more influenced by pCR than by the initial clinical status, including patients with positive axillary lymph nodes before the treatment[18,26].

The study ACOSOG Z1071[11] showed the feasibility of SLNB in initially positive axilla (cN1) which turned negative post NACT (ycN0)[11,13,27,28].

The current study revealed a possible correlation between the response of the breast primary tumor to NACT and the presence of axillary lymph nodes metastases after the treatment.

Table 4. Indicators of objective therapeutic response (complete or partial) of primary tumor and lymph node chain of women with breast cancer submitted to NACT

	Objective response breast		*p*-value	Objective response lymph node		*p*-value
	No	Yes		No	Yes	
Age						
Up to 45 years	3 (23.1%)	12 (41.4%)	0.252	7 (36.8%)	7 (30.4%)	0.661
More than 45 years	10 (76.9%)	17 (58.6%)		12 (63.2%)	16 (69.6%)	
T						
T2	6 (46.2%)	9 (31.0%)	0.344	5 (26.3%)	10 (43.5%)	0.292
T3	7 (53.8%)	20 (69.0%)		14 (73.7%)	13 (56.5%)	
N						
N1	7 (53.8%)	22 (75.9%)	0.154	15 (78.9%)	15 (65.2%)	0.327
N2	6 (46.2%)	7 (24.1%)		4 (21.1%)	8 (34.8%)	
ER						
No	6 (46.2%)	13 (44.8%)	0.936	5 (26.3%)	14 (60.9%)*	0.025
Yes	7 (53.8%)	16 (55.2%)		14 (73.7%)*	9 (39.1%)	
PR						
No	7 (53.8%)	13 (44.8%)	0.588	7 (36.8%)	13 (56.5%)	0.204
Yes	6 (46.2%)	16 (55.2%)		12 (63.2%)	10 (43.5%)	
HER2						
No	12 (92.3%)	22 (75.9%)	0.210	19 (100.0%)*	16 (69.6%)	0.011
Yes	1 (7.7%)	7 (24.1%)		0 (0.0%)	7 (30.4%)*	
Phenotype						
Luminal A	2 (15.4%)	1 (3.4%)	0.320	3 (15.8%)	0 (0.0%)	0.085
Luminal B	5 (38.5%)	16 (55.2%)		11 (57.9%)	10 (43.5%)	
HER2+	0 (0.0%)	2 (6.9%)		0 (0.0%)	1 (4.3%)	
Triple-negative	6 (46.2%)	10 (34.5%)		5 (26.3%)	12 (52.2%)	
Tumor grade						
I	2 (18.2%)	2 (7.7%)	0.384	4 (23.5%)	0 (0.0%)	0.056
II	6 (54.5%)	20 (76.9%)		9 (52.9%)	16 (80.0%)	
III	3 (27.3%)	4 (15.4%)		4 (23.5%)	4 (20.0%)	
LVI						
No	10 (90.9%)	24 (88.9%)	0.854	15 (88.2%)	19 (90.5%)	0.823
Yes	1 (9.1%)	3 (11.1%)		2 (11.8%)	2 (9.5%)	

Captions: T = tumor size; N = Lymph node; ER = estrogen receptor; PR = progesterone receptor: HER2 = human epidermal growth factor receptor 2; LVI = limphovascular invasion.
(*) $p < 0.05$ = Fisher's exact test or Pearson's chi-square test.
Note: Absolute and percent values

Patients with pCR of the breast presented pCR at lymph nodes 20.44-fold higher than patients who did not have the same response at the breast. The current analysis potentially indicates that if pathologic response at the breast occurs, SNLB is likely to be negative and avoided, in addition to potential sequelae and adverse effects, without interfering in the systemic treatment and local control of the disease.

Other factors associated with axillary response to NACT were analyzed as tumor size (T), axillary compromise (N), expression for progesterone receptor, estrogen receptor, HER2, phenotype (molecular subtype), tumor grade and presence of limphovascular invasion.

HER2-positive presented strong association – 36.42-fold higher – with the pCR in axillary lymph nodes when present. It was also expressed in the rate of pCR at the breast 12.50-fold higher than negative-HER2. The absence of estrogen receptor was another aspect interfering in the response rate of objective pathological response in lymph node, 4.36-fold higher in patients without the expression of this receptor.

Studies published earlier[18,29,30] showed that patients with triple-negative tumors and HER2-positive with negative axilla at the presentation and pCR at the breast post NACT, had low rate of positive SLNB (<2%), suggesting for these two tumor grades, a correlation

between pCR post NACT at the breast and negative SNLB in metastasis investigation.

None of the variables investigated in triple-negative tumors was significantly associated with pCR or objective at the breast or lymph nodes, different from the data published elsewhere.

Few are isolated tumor markers predictive of pCR found in the literature, but tumor expression of HER2, when associated with trastuzumab therapy and NACT reaches pCR of 65%[31]. The absence of expression of estrogen is another marker described associated with pCR rate[32]. Both factors influence the rate of pCR and concur with the data investigated herein.

In order to check the association of clinical N1 with sentinel lymph node post-neoadjuvant chemotherapy, it was observed whether the resected lymph node had the ultrasound-guided metal clip placed before the chemotherapy when FNAP was performed. The result revealed that the sentinel lymph node was clipped in 90.47% of the cases investigated. Unclipped lymph node revealed during SLNB may be attributed to the time since chemotherapy and possible displacement, similar to the literature[17,20,33].

FNAP and cytologic analysis to detect neoplastic cells at clinical N1 was positive in 68.8% of the cases. Every FNAP of suspected axillary lymph nodes of neoplastic compromise were ultrasound-guided.

The correlation between cCR and pCR reached only 52.9%.

The data about the tumor type and response to NACT allows to identify cases which tend to present negative sentinel lymph node and predict the absence of additional axillary metastatic disease, which, in these cases, may avoid SLNB and respective sequelae[18,34].

CONCLUSION

The pathological response at the breast, the presence of protein HER2 and absence of estrogen receptor on the primary tumor may predict good axillary response to NACT in naive-treatment patients with clinical staging T2-T3/N1-N2.

Other factors investigated as age, initial staging T and N, expression for progesterone receptor, Ki-67, molecular subtypes, tumor grade and presence of limphovascular invasion failed to show effects on the prediction of axillary response to chemotherapy.

The correlation of cCR with pCR was low and is unable to indicate any tendency of axillary surgical approach. pCR alone at the breast was the main factor related to negative investigation of axillary metastasis on sentinel lymph node.

The sample size was a limitation of the study which failed to respond to the research question, though it reinforces it: "Is it possible to avoid post-NACT sentinel lymph node biopsy in patients with pCR at the breast?"

Data about the prediction of pCR at the breast and axilla were presented by the study as well.

Statistically significant studies with larger samples with follow-up for a longer period to evaluate local relapse, DFS, GS and other outcomes for these patients are necessary.

CONTRIBUTIONS

All the authors contributed substantially to the study design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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