ORIGINAL ARTICLE
https://doi.org/10.29289/2594539420230002

Assessment of pathological response of breast cancer in patients undergoing neoadjuvant chemotherapy in a refferal hospital in Amazonas State

Kaiom Cesar Xavier Pacheco[1]*, Guilherme Vieira Pereira[2], Heitor Augusto de Magalhães e Silva[2], Henrique Vieira Pereira[2], Júlia Neves Becil[2], Kimberly Farias de Oliveira[2], Luana Izabela de Azevedo Carvalho[3], Márcio Henrique de Carvalho Ribeiro[4], Larissa Maria Contiero Machado[2], Lucas Barbosa Arruda[4], Isabela Abud de Andrade[4], Mariana de Mendonça Lima Ypiranga Monteiro[2], Thaís Cristina Fonseca da Silva[2], Hilka Flávia Barra do Espírito Santo Alves Pereira[2,5]

ABSTRACT

Introduction: The therapeutic options for breast cancer are diverse. Increasingly, treatments are established on an individual basis, depending on a series of variables ranging from age to the molecular profile of the tumor. When neoadjuvant chemotherapy (NAC) is necessary, adequate clinical evaluation (CE) and control examinations, such as breast ultrasound (US) and mammography (MMG), are of fundamental importance, as it is necessary to reevaluate the tumor lesion to determine an individualized surgical treatment, with the aim of performing breast-conserving surgery within the available techniques. This study sought to evaluate the pathological response of patients undergoing neoadjuvant chemotherapy, analyzing the presence or absence of tumor reduction by relating the physical examination with imaging methods (MMG and US), taking the anatomopathological examination measurements as the gold standard, thus intending to identify the best method for evaluating the pathological response. **Methods:** This was a prospective, observational, analytical cohort study. The study included 41 patients diagnosed with breast cancer detected by mammography and ultrasound (MMG and US) followed by biopsy, who underwent neoadjuvant chemotherapy (NAC) and surgery. The measurements of the malignant breast lesions obtained by CE, MMG and US were compared with the anatomopathological measurements on biopsy as the gold standard. **Results:** Pearson's correlation coefficient was the statistical method used for evaluation, finding a value of 0.49 between the anatomopathological examination and CE, 0.47 between the anatomopathological examination and MMG and 0.48 between the anatomopathological examination and US ($p<0.05$). **Conclusions:** CE, MMG and US showed a moderate correlation with anatomopathological measurement, in addition to a moderate correlation between them, demonstrating equivalence in the pre-surgical definition of the size of the breast tumor after NAC, being complementary to each other to define a measure of greater accuracy of the tumor in breast cancer.

KEYWORDS: mammography; ultrasound; clinical examination; neoadjuvant chemotherapy.

INTRODUCTION

Breast cancer is one of the challenges in the current scenario of population aging and combating chronic non-communicable diseases in Brazil[1]. It is the type of cancer that most affects women in the country, except for non-melanoma skin tumors, and also the one that kills the most[1]. According to Brazil's National Cancer Institute (INCA), about 73,610 new cases of breast cancer are expected in Brazil for the three-year period from 2023 to 2025, and in the case of the state of Amazonas, 500 new cases are expected per year, which corresponds to an estimated risk of 61.66 new cases for every 100 thousand women in Brazil[2,3]. The therapeutic options for breast cancer are diverse and range

[1]Fundação Centro de Controle de Oncologia do Estado do Amazonas, Department of Mastology – Manaus (AM), Brazil.
[2]Universidade Federal do Amazonas – Manaus (AM), Brazil.
[3]Universidade do Estado do Amazonas – Manaus (AM), Brazil.
[4]Universidade Nilton Lins – Manaus (AM), Brazil.
[5]Universidade Estadual Paulista – Botucatu (SP), Brazil.
***Corresponding author:** kaiomcesar@hotmail.com
Conflict of interests: nothing to declare. **Funding:** none.
Received on: 02/06/2023. **Accepted on:** 03/14/2024

from surgery and radiotherapy to systemic drug treatment (chemotherapy, hormone therapy)[4].

Neoadjuvant chemotherapy (NAC), that is, chemotherapy started before breast cancer surgery, was introduced in the 1970s, with the aim of reducing the stage of locally advanced (inoperable) disease and making it operable[5]. Since then, it has been gaining more and more ground, mainly in the presence of HER2-positive and triple-negative neoplasms associated with increased disease-free survival, and as a mechanism of tumor cytoreduction, which can occur partially or completely, allowing in some cases surgical procedures with greater preservation of breast tissue, so that the pathological complete response (pCR) after neoadjuvant treatment, in most cases, determines a better prognosis in the treatment of breast cancer[5,6].

Therefore, adequate clinical evaluation and performance of control examinations, such as ultrasound, mammography and MRI, are essential for the treatment of neoplastic breast lesions. The diagnostic accuracy of imaging tests to detect pCR is as high as 74% in MMG and 79% in US, with the former being more sensitive than physical examination, although less specific[7]. As for MRI, it is known that in addition to being the gold standard for evaluating response to NAC, it has been the most used to determine pCR in most studies[8-12].

This work was established as a method of elucidating clinical data in complementary association with imaging methods, in the quest to generate data with information that provides better monitoring for patients treated at the Fundação Centro de Controle de Oncologia do Estado do Amazonas (FCECON). Its objective was to evaluate the pathological response of patients undergoing NAC, analyzing tumor reduction and relating the size of the lesion through physical examination and the imaging methods MMG and US, taking the anatomopathological examination measurements as the gold standard, thus seeking to identify the best method to evaluate the pathological response in these patients in question. Although MRI is the gold standard test for evaluating pathological response, it was not applied in the study due to its unavailability in the Unified Health System (SUS).

METHODS

A prospective, observational, analytical cohort study was conducted. The study included 41 patients admitted to the Mastology Service of FCECON (Amazonas State Oncology Control Center Foundation) from May 1, 2021 to October 30, 2021; the patients were diagnosed with breast carcinoma and underwent NAC and surgery, where the metric results of malignant breast lesions acquired using CE, MMG and US methods after completion of NAC were compared, taking measurements from the anatomopathological examination as the gold standard.

CE was performed during hospitalization for the implementation of a surgical procedure, with the patient sitting in bed with her arms relaxed and loose at her sides to evaluate the armpits and supra- and infraclavicular fossae. Afterwards, the patient was positioned in a horizontal supine position with the arm above the head, using the oblique-lateral position when the nodules were in the lateral quadrants, close to the anterior axillary line. Therefore, the tumor was fixed between the examiner's fingers, who measured it using manual calipers. The size considered was the longitudinal and transversal measurement found. Regarding imaging examinations (US and MMG), these were analyzed both in relation to the report and in relation to the image, also using the largest tumor measurement as a reference for statistical evaluation.

All surgeries were performed by the FCECON Mastology Service, and pathological measurements were obtained by pathologists working at the service. In relation to the histopathological examination, the size of the tumor considered was the longitudinal and transverse measurement taken with a millimeter ruler in the macroscopic examination or, in cases where there was no visualization with the naked eye, through the largest measurement obtained by microscopic examination of the histological slide, being defined as zero when no neoplastic disease was observed in the surgical specimen. The acquired measurements were stored in a computerized database for later analysis.

The analysis of the drugs used in NAC was not the focus of this study, but the patients had standard treatment with doxorubicin, cyclophosphamide and paclitaxel, and when the c-erbB2 proto-oncogene expressed, trastuzumab was associated with the treatment, as well as double blockade with trastuzumab and pertuzumab in special cases.

Patients who did not undergo NAC and/or did not undergo control examinations after NAC were excluded.

For statistical analysis, Pearson's correlation coefficient (r) was used as a statistical analysis to evaluate the measurements obtained by each diagnostic method (CE, MMG and US and anatomopathological examination). The mean, median, standard deviation, minimum, maximum, absolute and relative frequency of data were also calculated to analyze the characteristics of the population. The data were presented in the form of tables, and $p<0.05$ was considered statistically significant.

The study was approved by the FCECON Research Ethics Committee (COEP) under No. 4.894.078.

RESULTS

In the group of 41 patients studied, the age ranged between 28 and 75 years, with a mean of 49 and a median of 47 years; only one patient was not Brazilian (2.4%), 23 patients (56%) were from the capital of Amazonas, while 13 (31.7%) were from the state's counteryside. Histopathological analysis by biopsy confirmed the diagnosis of malignancy in all 41 patients, with invasive ductal

carcinoma being the most common histological type, present in 85.3% of cases, as shown in Table 1.

Regarding the immunohistochemistry pattern, four cases were diagnosed as luminal A (9.7%) Ki-67 <14%, ten as luminal B (24.3%) KI-67 >14%, ten as hybrid luminal (24.3%), six pure HER2+ (14.6%) and eleven as triple-negative (26.8%).

The interval between the end of NAC and the surgical procedure was 57.1 days. The time elapsed between the evaluation of patients using work-up methods after NAC and surgery ranged from a minimum of 25 days to a maximum of 201 days, with a mean of 57.1 days and a median of 46 days. In three cases, the time between the end of NAC and surgery was more than 95 days, and in these cases, the delay was associated with personal reasons described by the patients, which increased the overall average attributed to the study.

The diameter of the lesions varied according to each method adopted, with ultrasound showing a lower standard deviation compared to the other findings (CE and MMG), according to Table 2.

The neoplastic lesions identified through CE, MMG and US were compared with the anatomopathological examination to determine which examination had the greatest association with the result found in the surgical specimen. Regarding CE, the tumor measurement was greater than that found in the anatomopathological examination in 46.3% of cases, being the same in 17% of cases, and lower in 36.5% of cases.

When analyzing the mammogram, the measurement found was greater than the anatomopathological measurement in 29.2% of cases, the same in 56% of cases and lower in 14.6% of the analyzed population. In the comparison for US, the lesion was larger than the pathological finding in 46.3% of cases, the same in 41.4%, and smaller in 12.1%.

Pearson's correlation coefficient was determined using the average between the longitudinal and transversal measurements of the tumor diameter obtained by the anatomopathological examination and for each preliminary examination conducted. The correlation coefficient found is highlighted in Table 3.

Pearson's correlation coefficients were also calculated between the non-surgical methods, obtaining r=0.40 for the comparison between CE and MMG, r=0.54 between CE and US, and r=0.41 between MMG and US, with all values being significant (p<0.005).

The pharmacological treatment used in NAC was through cycles of anthracycline + cyclophosphamide + taxane (AC x T) associated with trastuzumab in the presence of HER2+ tumors. Five patients underwent double blockade (trastuzumab and pertuzumab) combined with AC x T, and only two showed pCR.

The histopathological analysis of the surgical specimen identified residual presence of disease in 32 patients (78%); it was not possible to evaluate in 5 patients (12.1%) - Tx, and in 4 patients (9.7%), there was complete remission of the disease.

DISCUSSION

The individualization of therapies for the treatment of breast cancer is directly associated with technological advances, so that several imaging methods are used to define breast lesions, especially when it is necessary to assess the presence or absence of pCR. The present study sought to determine the best preliminary method to evaluate the pathological response to treatment with NAC in 41 patients, all women treated at a referral hospital in Amazonas State. Accordingly, the residual lesions were analyzed through physical examination and imaging methods (MMG and US), taking the anatomopathological examination

Table 1. Distribution according to histological type identified in the breast biopsy.

Histological type	n	%
Invasivo ductal carcinoma	35	85.37
Lobular	4	9.76
Metastatic adenocarcinoma	1	2.44
Mucinous	1	2.44
Total	41	100.00

Table 3. Pearson correlation coefficient (r) for comparison between anatomopathological examination and clinical examination, mammography and ultrasound (n=41). Correlation with statistical significance (p<0.05).

Correlation	R
Anatomopathological *versus* clinical examination	0.49
Anatomopathological *versus* mammography	0.47
Anatomopathological *versus* ultrasound	0.48

Table 2. Description of tumor size according to preliminary assessment.

Method	Tumor measurements (cm)				
	Mean	Standard deviation	Median	Minimum	Maximum
Clinical examination	3.5	4.1	2.9	0	16.1
Mammography	2.6	2.5	2.4	0	9.5
Ultrasound	2.4	1.9	2.2	0	11
Anatomopathological	2.8	3.4	1.6	0	14

measurements as the gold standard, demonstrating the equivalence of the methods in the pre-surgical determination of breast tumor size post-NAC.

There are several trials that have sought to verify the most reliable method for evaluating the pathological response of breast cancer after NAC. In these studies, a histological predominance of invasive ductal-type carcinoma is noted, with samples exceeding 60% in most of the articles evaluated, in agreement with the data we found, since 60.9% of our patients had histological involvement of the ductal type[5,6,8-11,13]. Regarding the immunohistochemical profile, the predominance of the luminal profile stands out, which was also evidenced in our study, where we observed this finding in 34% of patients[9,10,12-16].

NAC can be performed in any molecular profile, among which we can highlight tumors with expression of the c-erbB2 protein, which as a result of pharmacological advances has been associated with excellent results related to pCR, especially after the introduction of double blockade therapy (pertuzumab + trastuzumab)[15]. Of the 41 patients evaluated in our study, 32 (78%) showed no complete pathological response to neoadjuvant chemotherapy. When individualizing patients with c-erbB2 protein expression who underwent double blockade, we found two patients (40%) with pCR among the five who underwent treatment with trastuzumab and pertuzumab, a result that is similar to the findings described in the literature[14].

Analyses of measurements obtained through CE, MMG and US are also described in various publications; in some cases, in comparison with the findings of the anatomopathological examination, mostly determining the existence of a single method, superior to the others, for carrying out the evaluation of the pathological response to NAC[6-11,13]. Among the studies we analyzed, only one attributed MMG as a highly sensitive and reproducible method for evaluating the persistence of disease after NAC, with an accuracy estimated at 73%[7]. In our study, the mammogram showed lesions with a mean value equivalent to 2.6 cm, which is close to the mean value described in the anatomopathological analysis, in this case, equal to 2.8 cm, a finding that confirms the results of this study, indicating MMG to be a reliable method[7].

There is evidence of greater precision in measurements obtained through US when compared to those obtained through MMG, which is evidenced by various statistical methods[6,9,11,13]. As well as high accuracy when combined with MMG and US[7]. In our study, the diameter of the lesions varied according to each method used, with breast US having a lower standard deviation in relation to the other methods compared.

Pre-existing studies also confirmed a tendency for imaging methods to underestimate tumor size[6,10,17]. In the present study, this was verified in relation to CE, considering that imaging methods had less interference in measuring tumor size. There is evidence that CE could underestimate the size of the lesion, especially in circumstances in which the tumor is located in very deep regions, such as in large breasts or breasts that are very dense on palpation, which would make it difficult to distinguish between tumor and normal breast tissue. It can be inferred that we sought to minimize errors in relation to measuring the tumor during the physical examination, taking into account the rigor in positioning the patient correctly and using a millimeter ruler to better define the size of the lesion.

In recent years, no articles demonstrated CE, individually, to be the best method for evaluating the size of the residual tumor, when compared to imaging methods in relation to pathology. This fact is probably due to radiology evolution, which, through various methods, has been able to determine pathological response findings with greater precision through imaging tests[6-11,13-15,17]. It is interesting to note that when evaluating these studies, there is a lack of standardization in relation to the statistical evaluation method, thus using different correlation tests, which represent a difficulty in comparing results.

In our research, only two studies used Pearson's correlation coefficient to evaluate the pathological response: the first finding US to be the best method, with findings of 0.68[6]; the other demonstrating equivalence between the three evaluation methods, with a Pearson correlation coefficient of 0.8 between the anatomopathological examination and the CE, 0.7 between the anatomopathological examination and MMG, and 0.7 between the anatomopathological examination and US ($p<0.05$)[18]. In our study, we found a Pearson correlation coefficient equal to 0.49 between the anatomopathological measurement and that determined through physical examination; 0.47 when comparing the anatomopathological and MMG; and 0.48 between pathology and US ($p<0.05$).

In a study by Paris et al., the evaluation used was through the kappa index, which evaluated a similar relationship as ours with a coefficient of 0.4, not establishing superiority in relation to any method evaluated (US, MMG and CE), a finding also evidenced in our study[5]. We also found data associated with the interclass correlation coefficient, used to compare US and MMG in relation to MRI, finding superiority for the latter in this evaluation[9,11]. One hundred and seventy-four patients were statistically evaluated using the ROC curve with the aim of comparing the pathological response to NAC using MRI, CE and MMG, also demonstrating superiority in relation to MRI[10]. Spearman's correlation coefficient was also described in the search to compare the relationship between MRI, MMG and US, attributing superiority to MRI with a value of 0.786[15].

It is important to highlight that, despite the importance of all the methods used to measure the size of the tumor, MRI is increasingly presented as a more reliable method, being used as the main examination to evaluate pathological response[8-10,12,15]. In our search for articles for this discussion, we were forced to include MRI data due to the absence of publications that

exclude this imaging method from pathological response analysis. MRI was not introduced in our study because it is not possible in the context of the SUS, as it is not standard in the public health network, and it is not possible to use it as a comparison parameter with other imaging methods in the services of SUS.

Although this study evaluated preoperative measurements and the final tumor size, several limitations can be noted, among which the sampling data are shown, since it was a study with few patients, selection criteria, varying sizes of lesions, multiple histological types, and lack of comparison with the gold standard, namely MRI. Also, there were various chemotherapy regimens, types of cycles, and intervals between examinations, which were not performed on the same day but without a very long interval.

Despite all the limitations, we believe that the tumor measurements obtained by CE, MMG and US displayed a moderate correlation with that obtained by anatomopathological examination.

CONCLUSIONS

The results of this study demonstrate that tumor measurements obtained by CE, MMG and US displayed a moderate correlation with that obtained by anatomopathological examination, being similar in determining the size of the breast tumor after NAC, and complementary to each other to obtain a more accurate measurement of the tumor in breast cancer. Through these results, we can demonstrate the importance of this work in contributing to the treatment of patients diagnosed with breast cancer who undergo NAC and surgery.

AUTHOR'S CONTRIBUTIONS

KCXP: Investigation, Validation, Visualization, Writing – review & editing. GVP: Data curation. HAMS: Data curation. HVP: Data cration. JNB: Data curation. KFO: Data curation. LIAC: Data curation. MHCR: Data curation. LMCM: Data curation. LBA: Data curation. IAA: Data curation. MMLYM: Data curation. TCFS: Data curation. HFES: Investigation, Validation, Visualization, Writing – review & editing.

REFERENCES

1. Instituto Nacional de Câncer José Alencar Gomes da Silva. A situação do câncer de mama no Brasil: síntese de dados dos sistemas de informação. Rio de Janeiro: INCA; 2019.
2. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2023: incidência de câncer no Brasil. Rio de Janeiro: INCA; 2022.
3. Instituto Nacional do Câncer José Alencar Gomes da Silva. Estimativa Estado-Capital (Amazonas-Manaus) [Internet]. [cited on 2022 Oct 23]. Available from: https://www.inca.gov.br/estimativa/estado-capital/amazonas-manaus
4. Instituto Nacional de Câncer. Coordenação de Prevenção e Vigilância. Divisão de Detecção Precoce e Apoio à Organização de Rede. Dados e números sobre câncer de mama. Relatório anual 2022 [Internet]. [cited on 2022 Oct 23]. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files/media/document/dados_e_numeros_site_cancer_mama_setembro2022.pdf
5. Paris JF, Cimato G, Rolla EM, Saravia Toledo JA, León M, Salmoral L, et al. ¿Son el examen clínico, la mamografía y la ecografía métodos confiables para la valoración del tumor residual posterior a neoadyuvancia? Rev Argent Mastología. 2017;36(131):50-63.
6. Cortadellas T, Argacha P, Acosta J, Rabasa J, Peiró R, Gomez M, et al. Estimation of tumor size in breast cancer comparing clinical examination, mammography, ultrasound and MRI-correlation with the pathological analysis of the surgical specimen. Gland Surg. 2017;6(4):330-5. https://doi.org/10.21037/gs.2017.03.09
7. Zhang C, Kosiorek HE, Patel BK, Pockaj BA, Ahmad SB, Cronin PA. Accuracy of posttreatment imaging for evaluation of residual in breast disease after neoadjuvant endocrine therapy. Ann Surg Oncol. 2022;29(10):6207-12. https://doi.org/10.1245/s10434-022-12128-5
8. Kaise H, Shimizu F, Akazawa K, Hasegawa Y, Horiguchi J, Miura D, et al. Prediction of pathological response to neoadjuvant chemotherapy in breast cancerpatients by imaging. J Surg Res. 2018;225:175-80. https://doi.org/10.1016/j.jss.2017.12.002
9. Murakami R, Tani H, Kumita S, Uchiyama N. Diagnostic performance of digital breast tomosynthesis for predicting response to neoadjuvant systemic therapy in breast cancer patients: a comparison with magnetic resonance imaging, ultrasound, and full- field digital mammography. Acta Radiol Open. 2021;10(12):20584601211063746. https://doi.org/10.1177/20584601211063746
10. Scheel JR, Kim E, Partridge SC, Lehman CD, Rosen MA, Bernreuter WK, et al. MRI, clinical examination, and mammography for preoperative assessment of residual disease and pathologic complete response after neoadjuvant chemotherapy for breast cancer: ACRIN 6657 Trial. AJR Am J Roentgenol. 2018;210(6):1376-85. https://doi.org/10.2214/AJR.17.18323
11. Park J, Chae EY, Cha JH, Shin HJ, Choi WJ, Choi YW, et al. Comparison of mammography, digital breast tomosynthesis, automated breast ultrasound, magnetic resonance imaging in evaluation of residual tumor after neoadjuvant chemotherapy. Eur J Radiol. 2018;108:261-8. https://doi.org/10.1016/j.ejrad.2018.09.032
12. Rauch GM, Kuerer HM, Adrada B, Santiago L, Moseley T, Candelaria RP, et al. Biopsy feasibility trial for breast cancer pathologic complete response detection after neoadjuvant chemotherapy: imaging assessment and correlation endpoints. Ann Surg Oncol. 2018;25(7):1953-60. https://doi.org/10.1245/s10434-018-6481-y
13. Makanjuola DI, Alkushi A, Al Anazi K. Defining radiologic complete response using a correlation of presurgical ultrasound and mammographic localization findings with

pathological complete response following neoadjuvant chemotherapy in breast cancer. Eur J Radiol. 2020;130:109146. https://doi.org/10.1016/j.ejrad.2020.109146

14. Jones EF, Hathi DK, Freimanis R, Mukhtar RA, Chien AJ, Esserman LJ, et al. Current landscape of breast cancer imaging and potential quantitative imaging markers

of response in er-positive breast cancers treated with neoadjuvant therapy. Cancers (Basel). 2020;12(6):1511. https://doi.org/10.3390/cancers12061511

15. Sudhir R, Koppula VC, Rao TS, Sannapareddy K, Rajappa SJ, Murthy SS. Accuracy of digital mammography, ultrasound and MRI in predicting the pathological complete response and residual tumor size of breast cancer after completion of neoadjuvant chemotherapy. Indian J Cancer. 2022;59(3):345-53. https://doi.org/10.4103/ijc.IJC_795_19

16. Siqueira FMP, Rezende CAL, Barra AA. Correlação entre o exame clínico, a mamografia e a ultra-sonografia com o exame anatomopatológico na determinação do tamanho tumoral no câncer de mama. Rev Bras Ginecol Obstet. 2008;30(3):107-12. https://doi.org/10.1590/S0100-72032008005000005

17. Cuesta Cuesta AB, Martín Ríos MD, Noguero Meseguer MR, García Velasco JA, de Matías Martínez M, Bartolomé Sotillos S, et al. Accuracy of tumor size measurements performed by magnetic resonance, ultrasound and mammography, and their correlation with pathological size in primary breast cancer. Cir Esp (Engl Ed). 2019;97(7):391-6. https://doi.org/10.1016/j.ciresp.2019.04.017

18. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30. https://doi.org/10.3322/caac.21590