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Analysis of bilateral breast carcinomas: a profile of patients at a reference service

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ABSTRACT

Objective: To select cases of bilateral breast carcinoma (BBC) of patients seen at Hospital de Clínicas of Paraná, besides recognizing clinical and family characteristics, histological and immunohistochemical pattern, and incidences of synchronic/metachronic tumor in these patients. **Method:** Observational and analytical study of BBC cases of patients treated at Hospital de Clínicas of Paraná, from 2003 to 2019, developed from the analysis of medical records. **Result:** A total of 42 patients with BBC were selected. The incidence of BBC was 3.64%. All patients were women, mostly of white skin color and postmenopausal, with an average age of 51.82 years. Half patients showed a positive family history for cancer, with breast cancer present in 46%, ovarian cancer in 16%, and other topographies in 68%. In this sample, the synchronous tumor was present in 55% of patients, and the metachronous tumor, in 45%. Regarding patients' initial clinical staging, 61% had a locally advanced tumor at diagnosis. Both in the group of synchronic and metachronic tumors, the ductal subtype was the most frequent. Regarding the immunohistochemical subtype, patients in both groups had Luminal B tumors more frequently. In the group of metachronic tumors, the average time between the diagnosis of the first tumor and the second tumor was 5.68 years. **Conclusion:** In this sample, BBC is associated with a relevant family history, with a synchronic presentation pattern, from histology to ductal and immunohistochemistry to Luminal B as the most frequent.

KEYWORDS: Breast neoplasms; Synchronous neoplasm; Metachronous neoplasm.

INTRODUCTION

Bilateral breast cancer (BBC) is a rare clinical entity. Its estimated incidence is between 0.3% and 12%.[1] This neoplasm pattern can be considered synchronous, when it occurs simultaneously, or metachronous, when it is diagnosed from one month to a year after the primary tumor is found.[2,3]

The importance of studying BBC is due to the increased incidence of cases of breast carcinoma and its early diagnosis — which increases the survival time for these patients. However, the risk of developing contralateral breast cancer (CBC) is also increased. Patients who had early breast cancer treated have from two to six times greater chance of developing the contralateral neoplasia than the female population in general. The estimated risk is 0.4% to 0.8% per survival year.[4]

The relevance of BBC was first studied in 1956. The study showed that patients who treated breast cancer had from three to four times greater chance of developing bilateral cancer, which behaves as a primary tumor and not metastatic.[5]

There are several risk factors for bilateral breast cancer. Among them, the histological and immunohistochemical type, family history of breast cancer, genetic mutations, and age at diagnosis of the first cancer are the most important.[6,7]

The histological type most frequently associated with bilateral breast cancer is the lobular one. In the literature, the risk ranges from 1.42 to 6.55. According to the authors, this variation is due to the difference in biological behavior and tumor etiology.[8,9]

Family history is relevant in the following situations: a first or second degree family member with breast cancer before the age of 45, or two or more of these family members with this type of cancer before the age of 50; a family member with two or more breast cancers; an individual with ovarian, fallopian tube, or primary peritoneal cancer; male breast cancer; or three or more family members with cancer in the following types and/or topographies (especially if diagnosed at the age of 50 or before that): breast, pancreas, prostate (metastatic Gleason score 7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, colon, endometrium, thyroid, kidney, hamartomatous polyps of the gastrointestinal tract cancer, and an individual of Ashkenazi Jewish origin with breast, ovarian, or pancreas cancer at any age.[10]

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As to family history, the relative risk (RR) of increase in BBC was 2.8, especially for first-degree family members.[11] A study by Reiner et al. from 2013 showed that the risk of contralateral breast cancer for a 30- to 34-year-old patient with breast cancer without BRCA1 and 2 mutations and no family history is 7% in 10 years. Patients without genetic mutations, but with a second-degree relative with breast cancer, are at 9% risk; those with an affected first-degree relative have a 14.7% risk of contralateral breast cancer. A bilaterally affected family member increases the risk of a patient without a genetic mutation for contralateral breast cancer to 23.7%.[12]

Bilaterality suggests genetic origin, that is, hereditary breast cancer. There are pathogenic mutations associated with this type of cancer, especially in BBC, which are: BRCA1 and BRCA2 (50%–85%), PALB2 (33%–58%), TP53 (Li-Fraumeni syndrome, 50%–90%), PTEN (Cowden syndrome/PTEN Hamartoma Tumor Syndrome, 25%–50%), STK11 (32–54%), and CDH1 (30%–50%).[12,13] The most important mutation related to bilateral neoplasm is BRCA1 and BRCA2. A population study with 705 women with BBC — with a mutation in the BRCA 1 and 2 genes — showed that the risk of bilateral neoplasia was 4.5 and 3.4 in BRCA 1 and 2 mutations, respectively, and the estimated cumulative risk over 10 years was 18.4 with the mutation and 4.8 without it.[13]

The patient's age at diagnosis of the primary tumor is a significant factor for bilateral cancer, especially for patients under 50 years old.[14] In a study carried out in Sweden with 1,351 cases, patients over 50 years old had an RR of 1, whereas those under 50 had an RR of 9.9.[15]

The objective of the present study was to assess the clinical, familial, histological, and immunohistochemical pattern of patients with bilateral breast cancer for a better understanding of this clinical entity, which, although rare, is of great importance.

METHODOLOGY

This is a cross-sectional, retrospective, observational, and analytical study. The target population analyzed is patients treated by the tocogynecology service of Hospital de Clínicas of Universidade Federal do Paraná, from January 2003 to December 2019. Patients with unilateral breast carcinoma, breast cancer whose histology did not confirm breast carcinoma, breast cancer resulting from metastasis from another primary site, and patients with information reported in their medical records in an incomplete, inconsistent, incomprehensible, or misplaced medical record were excluded.

Based on the analysis of medical records, data relating to clinical and family characteristics, histological and immunohistochemical pattern, time of diagnosis of contralateral neoplasia (synchronic/metachronic), and the type of treatment used in metachronic tumors were obtained and recorded. After that, data were grouped into spreadsheets in Microsoft Office Excel® (2016), with subsequent data analysis by the researchers.

Research waives the Free and Informed Consent Term because it is a project with simple analysis of medical record data, without direct or minimal interference in patients.

The present study was approved by the Research Ethics Committee of Hospital de Clínicas, Universidade Federal do Paraná, with Presentation Certificate for Ethical Appreciation (CAAE) No. 11701819.9.0000.0096.

RESULTS

A total of 42 patients with BBC was selected out of 1,523 patients seen at the tocogynecology service of Hospital de Clínicas of Universidade Federal do Paraná, of which four were excluded due to lost medical records or incomplete information on them. The incidence of BBC in the surveyed period was 3.64%. All patients are women with a mean age of 51.82 years. White skin color is the most prevalent (82%), followed by ***parda*** (11%), and black (8%). The mean menarche age of patients was 12.89, ranging from 10 to 18 years old. As to menopausal status, 42% are pre-menopausal and 58% post-menopausal, with an average age of menopause of 48, ranging from 39 to 56. Regarding pregnancy, 16% of the patients are nulligravida, 8% had one pregnancy, 32% had two pregnancies, and 45%, three or more. Half patients have a positive family history for neoplasm, with breast cancer present in 46%, ovarian cancer in 16%, and neoplasms of other topographies in 68%. Neoplasms of other topographies are distributed as follows: gastrointestinal tract with 21%, non-ovarian gynecological with 16%, urological with 16%, hematological with 11%, and head and neck with 5%. Smoking history was present in 29% of patients, with an average burden of tobacco-related conditions of 27.36. Patients' mean body mass index (BMI) was 28.08.

In this sample, the synchronous tumor was present in 55% of patients, whereas the metachronous tumor, in 45%. Regarding the patients' initial clinical staging, 61% presented with locally advanced tumor (stage IIb) at their first medical appointment.

Exclusively to the group of synchronous tumors, the mean age of patients was 52.14, distributed as follows: less than 40, 14%; between 40 and 49, 38%; between 50 and 59, 19%; older than 60, 29%. The ductal histological type was the most frequent (93%), followed by the lobular type (7%). Of the patients, 60% had moderately differentiated tumors. With respect to immunohistochemical subtype, most patients had luminal B tumors (43%), followed by HER2 (29%), triple negative (24%), and luminal A (5%). Comparing the histological and immunohistochemical profile of each breast, 62% agreed and 48% were not the same.

Exclusively to the group of synchronous tumors, the mean age of patients was 51.41, distributed as follows: less than 40, 24%; between 40 and 49, 12%; between 50 and 59, 47%; older than 60, 18%. The average time between the diagnosis of the first tumor and the appearance of the second was 5.68 years. The most common histological type was ductal carcinoma in 73%, followed by lobular carcinoma in 11%, medullary carcinoma in 9%, and metaplastic carcinoma in

7%. Regarding the immunohistochemical profile, the most prevalent was luminal B in 32%, luminal A in 29%, triple negative in 24%, and HER2 in 15%. The histological and immunohistochemical profile of each breast was equal in only 29% of patients, who had a triple negative in 60% and luminal B in the other 40%. When assessing treatment in the primary tumor, 41% of patients underwent neoadjuvant therapy (86% with standard chemotherapy and 14% hormone therapy), 53% underwent conservative surgery, and 73%, axillary lymphadenectomy. Of the patients, 67% had their tumors irradiated, and 87% performed adjuvant therapy according to their tumor profile.

DISCUSSION

Bilateral breast carcinomas (BBC) are rare cancer events. In the present study, despite the small sample, half patients have a positive family history from the oncological point of view, of which 46% are in breast topography and 16%, in ovarian topography, reiterating the importance of this risk factor, which has been well described in the literature.[10,11]

In research, 55% are synchronous tumors. Upon diagnosis, neoplasm showed to be locally advanced, that is, above stage IIb. On the other hand, synchronic cancer represents 1% of the total, and metachronic cancer is seven times more frequent in the literature.[16] This is probably due to the small sample size and the quality of the health system offered to this selected group.

Regarding patients' age, the trend in the two groups is different, although the average age is quite similar. In the synchronic ones, 52% of the sample is made up of women under 50 years old, whereas in the metachronic ones, 65% was above that age.

As for the histological subtype and the tumor grade, the study results were like those found in unilateral carcinomas. Both in the synchronous and metachronic groups, positive hormone receptor tumors were the most frequent. In the literature, the profile of the highest risk for bilateral breast cancer is that of negative hormone receptors, as in a study with 4,036 patients who presented that the risk of developing another tumor bilaterally was 10 times greater in negative receptors.[17]

Besides that, in the synchronic group, 52% of the patients had HER2 or triple negative tumors, that is, those potentially more aggressive tumors, whereas in the metachronic group the immunohistochemical profile was similar to the distribution of unilateral breast tumors. The aggressiveness and the worse prognosis of bilateral tumors is described in other articles. Bilateral tumors have lower survival disease-free, and high rates of lymphatic spread and distant metastasis.[18] According to a study carried out with 1,705 patients, the rates of local recurrence in five and 10 years were 4.5% and 9.1%, respectively, for patients with bilateral cancer; *versus* 3.3% and 7.6%, respectively, for unilateral cancer. In 10 years, the rates of distant metastases were 26.9% and 50.7% for unilateral and bilateral cancer, respectively. Survival in five and 10 years was 82.1% and 41% in patients with bilateral cancer, respectively, and 91.4% and 84% for unilateral cases.[16]

When comparing the samples from each breast in the metachronous group, most were discordant in relation to the histological and immunohistochemical profile. This generates an interesting caveat which is that when treating a bilateral tumor, we must often approach it as a second primary tumor.

Although this is a rare pathology, there is a description of an important tool to prevent the development of BBC in the literature: contralateral risk-reducing mastectomy. However, this is beneficial only for high-risk patients regarding the development of BBC, which includes patients with known BRCA1, BRCA2, TP53, PTEN Gold mutations, and/or family history suggestive of the tumor's genetic origin,[7,19,20] especially for young patients with triple negative tumors and with good response to neoadjuvant therapy.[6]

In a Mayo Clinic study, 214 women classified as high risk and 425 classified as moderate risk underwent bilateral mastectomy. During a 14-year follow-up period, seven breast cancers were diagnosed, which represented a 90% risk reduction compared to the expected number of neoplasms in this topography.[21]

A prospective analysis in the Netherlands evaluated 583 women with a BRCA mutation between 1980 and 2011, selected from a multicenter cohort. Of these, 242 (42%) underwent contralateral mastectomy and 341 (58%) were under observation. BBC was detected in four patients (2%) after contralateral mastectomy and in 64 patients, in the observation group (19%).[22]

The largest prospective analysis of breast cancer after bilateral mastectomy, called the PROSE study and conducted in 2004, evaluated 2,484 women with BRCA1 and BRCA2 mutations and of 22 centers in the United States and Europe. No breast cancer was diagnosed in the 247 women who underwent bilateral mastectomy, whereas 98 breast cancers (7%) were diagnosed in the group of those under observation, during the three-year follow-up.[23]

Further studies are needed to better clarify the clinical, familial, histological, and immunohistochemical pattern of bilateral breast carcinomas, which, although rare, are of great clinical importance.

CONCLUSION

BBC is rare and is associated with a relevant family history. The most frequent pattern was ductal carcinoma with luminal subtype B. In this sample, the synchronic type was the most common.

AUTHORS' CONTRIBUTIONS

C.V.P.: conceptualization, research, methodology; data acquisition; statistical analysis, data interpretation, article writing, article review; B.R.B.: data acquisition, data interpretation, article writing; L.R.B.: conceptualization, research and methodology, data interpretation, article review; M.N.A.: data acquisition, data interpretation; V.M.B.: conceptualization, investigation, methodology, data interpretation, article review.

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ORIGINAL ARTICLE
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Tumor biological profile of patients up to 50 years of age in a countryside city of São Paulo

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ABSTRACT

Introduction: In Brazil, breast cancer screening is not performed in young women. However, although less frequent, the disease is generally more aggressive in this age group, with worse prognosis and refractoriness to treatment. Thus, the identification of specific subtypes by immunohistochemistry can help improve the effectiveness of treatments. **Objectives:** To evaluate the biological characteristics of breast tumors in patients under 50 years. **Methods:** This is an observational, longitudinal, retrospective study, based on data collected from medical records of the Hospital do Câncer de Franca, from January 2015 to February 2018. **Results:** The most frequent biological subtype was luminal B (42.5%), and the mean age of the women was 43.6 years. The most prevalent clinical staging was IIA (31%). Mastectomy with axillary drainage was the most used surgical treatment. A positive correlation was found between biological profiles and sociodemographic data, with a predominance of the luminal B subtype in women under 40 years and luminal A in those between 41 and 50 years. The mean tumor size was 4.2 cm, being larger in older and white patients. In multiparous women, the subtypes HER2 and luminal A and B stood out. **Conclusion:** Luminal B and luminal A biological profiles, as well as staging II and III, were the most prevalent. Mastectomy and axillary drainage were the most common surgical treatments. The employment of these procedures should be reviewed by the service in order to improve the quality of life of the patients treated, favoring the expansion of primary conservative surgeries or post-neoadjuvant chemotherapy.

KEYWORDS: breast neoplasms; screening; immunohistochemistry.

INTRODUCTION

Currently, breast cancer is the subject of many scientific discussions about screening and treatment due to its high incidence and for being the main cause of cancer death among women in Brazil and worldwide[1]. The worldwide incidence is approximately 1.7 million, representing the second most common type of cancer in women[2]. In Brazil, according to the National Cancer Institute (*Instituto Nacional de Câncer* – INCA), the estimated incidence for 2020 is 66,280 new cases (61.61 cases for every 100,000 women), with the state of São Paulo having an estimated rate above the national, 81.06 cases for every 100,000 women[2].

This neoplasm is more prevalent in women over 50 years of age. However, when it affects younger women, it tends to have a more aggressive clinical presentation and a worse prognosis[3-5], which may be associated with factors such as late diagnosis, since they do not fit the target population of screening programs, as well as the tumor molecular characteristics.

Although breast cancer is less prevalent in young women, the likelihood of its development increases with age. The incidence of invasive breast tumors published by the Surveillance, Epidemiology, and End Results (SEER) Program between 2013 and 2017 was 1.9% for individuals aged 20–34 years, 8.3% for 35–44 years, and 19.7% for 45–54 years[6].

In Brazil, mammographic screening should be performed every 2 years in women aged 50 to 69 years, according to the Ministry of Health. Nonetheless, the American Cancer Society (ACS) recommends annual screening for individuals aged 45 to 54 years and biannual for those over 55 years. Women between 40 and 45 years of age are also free to have annual screenings if they so choose. In addition, ACS recommends bringing the screening forward for women at high risk of developing the disease, with mammography and breast magnetic resonance imaging (MRI) after the age of 30. This group includes women with mutations in the *BRCA1* and *BRCA2* genes; first-degree relatives with a known mutation in these genes; at 20% to 25% risk of developing

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the disease, as estimated by specific models of risk calculation (BRCAPRO, Claus, BOADICEA — Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, and Tyrer-Cuzick); those with genetic diseases (Li-Fraumeni, Cowden, and others); or who had chest wall irradiation before the age of 30[7].

The psychosocial issue is one of the most relevant after diagnostic confirmation in young patients, involving specific problems related to the preservation of fertility, pregnancy, and lactation, in addition to body image and sexuality. For this reason, these cases deserve a differential and individualized approach before the start of any therapeutic decision, since they can have long-term consequences, such as infertility and psychological disorders, such as anxiety and depression. This approach should be continuously discussed throughout the medical follow-up, in a multidisciplinary way[4,8,9].

Among the risk factors for disease recurrence directly related to prognosis, the following stand out: tumor size, lymph node involvement, proximity to surgical margins after resection, and classification of the tumor molecular subtype[3]. The immunohistochemical evaluation can identify four different groups of tumors related to the expression of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2). They are luminal A, luminal B, triple-negative, and HER2[10,11].

The expression of estrogen and progesterone receptors characterizes the luminal A and B subtypes, which favor endocrine treatment, in general, and have a more favorable prognosis. The expression of epidermal growth factor receptor 2 may be present in the luminal B subtype and is the main characteristic of the HER2 subtype, which does not show hormone receptor expression, leading to greater biological aggressiveness. Triple-negative tumors do not express hormone receptors and epidermal receptor 2. The "baseline-like" type has an overexpression of cytokeratins (CK5, CK6, and CK14) and epidermal growth factor receptor (EGFR)[12].

The prevalence of each subtype varies according to age, ethnicity, and behavioral aspects. Biological behavior in young women tends to be more aggressive, with unfavorable clinical evolution, greater local recurrence and distance from the disease, in addition to being associated with several genomic instabilities related to molecular subtypes, especially triple-negative, basaloid, and HER2+[13].

Thus, besides determining the classic prognostic and predictive factors, such as clinical and imaging staging to assess tumor size, lymph node involvement, and distant metastasis, the molecular classification of the disease must also be carried out in order to provide the most specific treatment for each case, seeking to control recurrences and overall disease-free survival[13]. Thus, this study aims to evaluate the tumor biological profiles of women aged outside the target population of mammographic screening practiced in Brazil, undergoing surgical treatment in an inland city of São Paulo.

MATERIALS AND METHODS

This is an observational, longitudinal, retrospective study, based on data collected from medical records of the Hospital do Câncer de Franca.

Inclusion criteria

Patients under 50 years of age who underwent surgical treatment at the Hospital do Câncer de Franca from January 2015 to January 2018 were included.

Exclusion criteria

Patients over 50 years of age who underwent surgical treatment and those under 50 years who were not submitted to surgical treatment were excluded.

Statistical analysis

The data obtained (demographic characteristics, initial staging, diagnostic approach, type of surgery, and adjuvant therapies) were entered into an Excel® spreadsheet and subsequently submitted to statistical analysis, represented descriptively in graphs and tables. A comparative analysis between tumor biological profiles, demographic data, and initial staging was also performed, with $p<0.05$ being considered significant.

Ethical aspects

The project was submitted for consideration and approval to the Research Ethics Committee of Fundação Santa Casa de Misericórdia de Franca, following the guidelines and regulatory standards for research involving human beings established by resolution 4662012.3, and was approved under registration number 09441219.0.0000.5438.

RESULTS

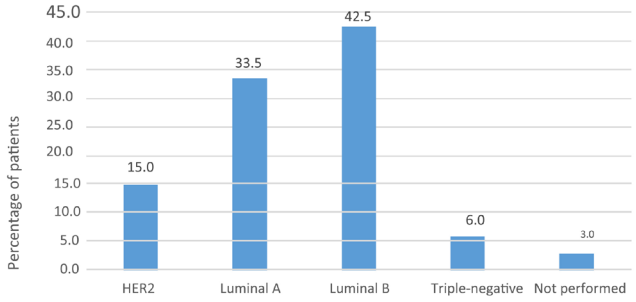
The sample consisted of 34 women under 50 years of age diagnosed with breast cancer, treated at the Hospital do Câncer de Franca from January 2015 to February 2018.

The immunohistochemical analysis of the studied population revealed that the most frequent tumor subtype was luminal B (42.5%), followed by luminal A (33.5%), HER-2 (15%), and, finally, triple-negative (6%), as shown in Graph 1.

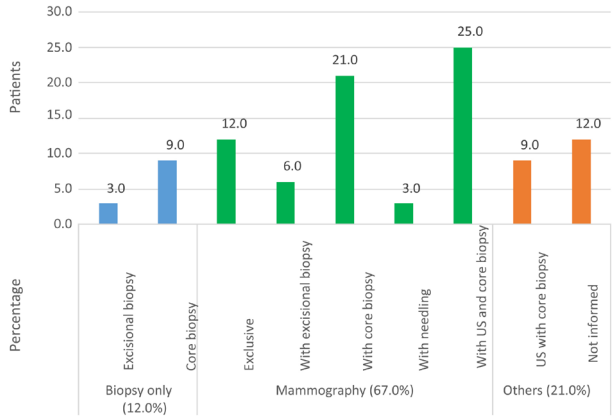
Demographic variables are described in Table 1, and the results of mammographic exams in the first appointment in Table 2.

The interval between the first appointment and the surgical treatment was 101±79.5 days (standard deviation – SD). Graph 2 represents the complementary diagnostic tests performed in these patients in the service during this period. Those who only had a mammogram underwent a previous biopsy in another service; therefore, all patients submitted to surgery had a prior histopathological investigation.

Graph 3 presents the distribution of cases according to clinical staging.

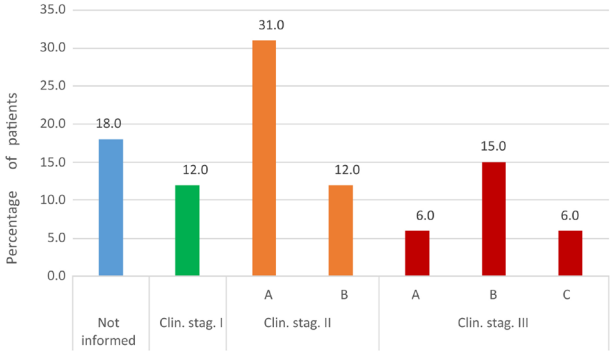


Graph 1. Percentage of patients according to tumor subtype.



US: ultrasound.

Graph 2. Complementary diagnostic tests performed (%).



Clin. stag.: Clinical staging.

Graph 3. Clinical staging of patients (%).

Table 1. Epidemiological characteristics.

Epidemiological characteristics of the sample		
Age (years)	Minimum	28
	Median	45
	Maximum	50
Ethnicity (%)	White	79
	Multiracial	15
	Black	6
Marital status (%)	Married	73
	Single	9
	Divorced	15
	Widow	3
Parity (%)	Nulliparous	3
	Multiparous	54.5
	Primiparous	9
	Not informed	33.5
Origin (%)	State of São Paulo	27.5
	Franca	39.5
	State of Minas Gerais	15
	Other states	18

Table 2. Mammographic BI-RADS in the first appointment.

Mammographic results in the first appointment (%)	
BI-RADS® 0	6
BI-RADS® 1 and 2	6
BI-RADS® 3	6
BI-RADS® 4	24.5
BI-RADS® 5	15
BI-RADS® 6	6
No data in the medical record or no previous exam	36.5

After the histological diagnosis, the immediate procedures adopted were surgery (57.5% of cases), neoadjuvant chemotherapy (CT) (39.5%), and adjuvant CT (3%). Among the patients whose treatment was surgical, 73% were submitted to radical mastectomy and 27% to conservative procedures. Regarding the axillary approach, drainage was performed in 67% of women and sentinel lymph node biopsy in 18%. In 3% of them, there was no research on the lymph node chain, and in 12%, this information was not in the medical records. The high rate of mastectomy may be associated with the high percentage of locally advanced tumors (≥IIB), the unfavorable relationship between tumor size and breast volume at the initial physical examination, and/or the option made by the patient, even after specialized guidance on the safety of conservative surgeries, which may also justify the low number of referrals for conservative procedures after neoadjuvant CT.

Despite the small sample size, multivariate analysis was performed between tumor characteristics and demographic data (age and ethnicity), as well as between tumor biological profiles and demographic data of the studied group.

Table 3. Relationship of biological subtypes with age group.

Age group (years)	Biological subtype (n)					Total
	Luminal A	Luminal B	HER2	Triple	Others	
≤40	0	6	1	0	1	8
41–50	11	7	4	2	1	25
Total	11	13	5	2	2	33

The mean tumor size was 4.2±2.8 cm (SD). A positive relationship was found between this variable and age (r=0.4; p=0.034), that is, the older the woman, the larger the tumor. The same happened with ethnicity – the tumor size was larger in white women compared to multiracial and black women (r=0.6; p=0.004).

No significant association was detected between biological profiles and ethnicity (χ^2=1.83; p=0.40) or origin (χ^2=1.40; p=0.706). However, a positive relationship was identified with parity, namely, the prevalence of HER2, luminal A, and luminal B tumors was higher in multiparous women (χ^2=11.67; p=0.009), and also with age (χ^2=9.49; p=0.08), as shown in Table 3. The luminal A subtype was predominant in the age group 41 to 50 years (p<0.02). No statistical significance was found in the number of triple-negative cases among patients under 40 years of age.

DISCUSSION

The investigation of molecular subtypes in this sample demonstrated the predominance of luminal B (42.5%), followed by luminal A (33.5%). In a recent population study in the US, DeSantis et al. revealed that the number of triple-negative cases decreased by 1.5% to 2.6% in all ethnic groups and age groups in the period studied. The reason is unclear but may be related to the change in risk factors associated with different hormonal subtypes, such as parity, which has been decreasing in developed countries and is connected with triple-negative subtypes[13]. Conversely, in our multivariate analysis, multiparous women presented higher rates of tumors with receptor expression, which may be associated with the low sample size or the fact that they belong to a greater age range within this subgroup. The results of this study are compatible with the national survey carried out in 2014 by Carvalho et al., with more than 5,500 breast tumor samples from the 5 geographic regions. In the survey, they addressed the regional differences in the presentation of molecular subtypes of breast cancer, reporting a higher prevalence of luminal A and B subtypes in the Southeast and South regions of Brazil, even when analyzing age subgroups divided into older and younger than 50 years. They also found that the prevalence of triple-negative tumors was higher in the Northern region of the country. This difference in distribution can be explained by the diversity and heterogeneity of ethnic groups, eating habits, urbanization, climate, and access to health systems in Brazil[14].

The prevalence data on the subtypes that express hormone receptors in this age group are also corroborated by the study by Olivieri et al., who analyzed histological samples from pre-menopausal Latin patients, using partial data from the PRECAMAMA study[15], and also identified a higher incidence of the luminal A subtype (58%), followed by triple-negative (21%), luminal B (11%), and HER2 (5%). Despite the similarity of the subtypes found in the post-menopausal period, they detected a greater expression of Ki-67, even in the luminal A subtype, and specific gene mutations in oncogenes, as in the *TP53* gene, which could explain the differences in prognosis of these age groups[16].

Regarding ethnicity, Clarke et al. analyzed the distribution of breast cancer subtypes in more than 90,000 patients in California and reported that black women had higher triple-negative rates at all ages[17]. This study found no significant differences between subtype distribution and ethnicity, which may be associated with the sample size and the ethnic diversity of our population.

We identified a low rate of patients in clinical staging I (12%) and 70% in staging II and III, with 39% being locally advanced (above IIB). We also observed that medical records lacked this information in 18% of cases, which will be used as a warning for the professionals responsible. Among the possible explanations, we highlight the failure to perform routine mammography in patients under 50 years of age. In this age group, mammographic screening is not recommended by the Brazilian Ministry of Health national guidelines. In a recent systematic review of the cost-effectiveness of breast screening programs, Mandrik et al. showed evidence of the benefits of screening individuals aged 50 to 69 years. However, before 50 and after 70 years, other factors should be considered, such as population characteristics of disease incidence and organizational structure of health systems[18]. In addition, European clinical trials on the subject also question the real effectiveness of screening in this age group in decreasing mortality from the disease, given the lower sensitivity and specificity and the higher proportion of false-positive results and biopsies performed unnecessarily[19].

In 2013, a national study carried out with more than 12,000 breast cancer patients under 40 years of age (mean age 36 years) also found a higher prevalence of IIA staging[1]. Similar data were presented by Stival et al., who detected a higher frequency of IIA and IIB tumors in patients aged between 40 and 50 years, with no significant differences in individuals over 50 years[20].

The time between visiting the service and surgical treatment was longer than that recommended by the Ministry of Health (60 days)[21] and may be associated with the disproportion between the demand for care and the organizational structure of the service.

Concerning surgical treatment, some services still tend to perform a greater number of radical surgeries (mastectomies) in younger patients to the detriment of conservative procedures, as observed in this study, in which only 27% of patients were

submitted to conservative treatments. Moreover, the rate of patients referred to neoadjuvant CT was relatively low (39.5%), and these individuals are potential candidates for conservative surgery later. This finding can be explained by particular decisions between the staff physicians and their patients or by the lack of closer integration between the clinical oncology, mastology, and plastic surgery teams. No data were collected on the breast reconstructions performed, which, due to the structuring of the teams, are usually done late, in the second surgical period. Both conservative surgery and mastectomy are well-established local treatments for invasive breast carcinomas, and several randomized clinical trials with a follow-up of more than 20 years have shown that conservative surgery is safe and has outcomes equivalent to mastectomy as to overall disease-free survival in stages I and II[22]. In 2010, Veronesi et al. revealed that the cumulative risks of local recurrence after conservative surgery followed by radiotherapy would be acceptable in ten years (12%), and, therefore, age should not be a determining factor for surgical recommendation, which should be based on the oncological safety defined by the tumor/breast ratio and a favorable cosmetic result[23]. In more recent studies, the recurrence after conservative surgery and subsequent adjuvant treatment decreased to 5.2% and 8.7%, according to protocols of the National Surgical Adjuvant Breast and Bowel Project (NSABP), in tumors without and with axillary involvement, respectively[24,25]. In addition, several studies report that the recurrence rate is associated with different molecular subtypes, being higher in triple-negative tumors and those with overexpression of HER2[22]. We emphasize the importance of performing an appropriate preoperative screening with imaging tests (especially mammography and breast ultrasound, as well as MRI when necessary) to rule out multicentric tumors, which would make conservative procedures contraindicated[25].

Thus, the immunohistochemical profile of this group of patients and the initial staging were similar to those of older age groups, according to the literature review. This finding also points to a worse prognosis of the disease at younger ages, possibly associated with complex factors of tumor genetic instability, whose knowledge is in progressive construction and will increasingly expand the individualization of therapeutic possibilities.

CONCLUSION

The most prevalent biological profiles in this sample of patients aged under 50 years were luminal B and luminal A subtypes and staging II and III. Mastectomy and axillary drainage were the most common surgical treatments. The employment of these procedures should be reviewed and rethought by the service in order to improve the quality of life of the patients treated, favoring the expansion of primary conservative surgeries or post-neoadjuvant chemotherapy.

AUTHORS' CONTRIBUTIONS

M.R.C.: data curation, formal analysis, investigation, writing – original draft; K.A.C.: conceptualization, investigation, methodology, investigation, project administration, supervision, validation, visualization, writing – review & editing; B.M.K.: data curation, formal analysis, investigation, writing – original draft; S.S.M.: data curation, formal analysis, investigation, writing – original draft; R.T.S.: methodology, validation, writing – review & editing.

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ORIGINAL ARTICLE
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Postoperative complications following simultaneous therapeutic and contralateral prophylactic nipple-sparing mastectomy: a retrospective study

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ABSTRACT

Introduction: Nipple-Sparing Mastectomy (NSM) is increasingly indicated for therapeutic and prophylactic purposes due to better cosmetic results with nipple maintenance. Postoperative complications have not been compared among patients who have undergone simultaneous therapeutic and contralateral prophylactic NSM. The aim of the present study was to evaluate the incidence and risk factors for postoperative complications in bilateral/unilateral NSMs, and therapeutic and/or prophylactic NSMs. **Methods:** Retrospective study of patients who underwent NSM between 2007 and 2017 at A.C. Camargo Cancer Center. **Results:** Among 290 patients, 367 NSMs were performed, 64 simultaneous therapeutic and contralateral prophylactic NSM. The latter were associated with more postoperative complications (OR=3.42; p=0.002), mainly skin flap necrosis (OR=3.79; p=0.004), hematoma (OR=7.1; p=0.002), wound infection (OR=3.45; p=0.012), and nipple-areola complex (NAC) loss (OR=9.63; p=0.003). Of the 367 NSMs, 213 were unilateral NSMs, which were associated with lower rates of postoperative complications (OR=0.44; p=0.003), especially skin flap necrosis (OR=0.32; p=0.001), hematoma (OR=0.29; p=0.008), wound infection (OR=0.22; p=0.0001), and reoperation (OR=0.38; p=0.008). Obesity was related to more postoperative complications (OR=2.55; p=0.01), mainly hematoma (OR=3.54; p=0.016), reoperation (OR=2.68; p=0.023), and NAC loss (OR=3.54; p=0.016). Patients' age (p=0.169), their smoking status (p=0.138), breast ptosis (0.189), previous chest radiotherapy (p 1), or previous breast surgery (p=0.338) were not related to higher chances of postoperative complications. **Conclusions:** Results suggest that performing therapeutic and contralateral prophylactic NSM as separated procedures may represent a good strategy for minimizing postoperative complications.

KEYWORDS: subcutaneous mastectomy; postoperative complications; breast cancer; prophylactic mastectomy.

INTRODUCTION

Nipple-sparing mastectomy (NSM) consists of remove the mammary gland while preserving the skin envelope and the nipple-areola complex (NAC).[1] The main advantage of preserving the NAC during NSM is to achieve better cosmetic results.[2,3] However, this approach has been associated with postoperative complications in 12.4% – 53.7% of cases.[2,4-13] The main postoperative complications associated with NSM include skin flap necrosis, NAC necrosis, wound infection, wound dehiscence, implant removal due to infection or dehiscence, and hematoma which requires drainage.[2,4-13]

NSM can be offered in different scenarios: bilateral risk-reducing (prophylactic) NSM for women who carry a genetic mutation which confers a higher risk of breast cancer; bilateral therapeutic NSM for patients with synchronous bilateral breast cancer; bilateral therapeutic NSM and contralateral prophylactic NSM for patients who carry a genetic mutation which can develop into breast cancer; unilateral therapeutic NSM; and unilateral prophylactic NSM. Previously, postoperative complications between bilateral and unilateral NSM,[7,13] and between therapeutic and prophylactic NSM[3,6,11] have been examined. However, to date, all of the scenarios listed above have not been compared. Therefore, the

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aim of the present study was to compare postoperative complications of bilateral or unilateral NSM, and prophylactic and/or therapeutic NSM, and determine which risk factors are associated with NSM's postoperative complications.

MATERIALS AND METHODS

This retrospective study examined patients who underwent NSM at A.C. Camargo Cancer Center between January 2007 and December 2017. Male patients, patients treated at another institution, and patients whose data could not be retrieved from medical records were excluded. Prophylactic NSM was considered for patients without breast diseases or with a previous biopsy of Lobular Carcinoma *in situ*. Therapeutic NSM was considered for treatment of ductal carcinoma *in situ* and invasive carcinoma. Both sides of bilateral NSM were performed by the same team of surgeons. Postoperative complications considered were those that appeared within 90 days of surgery. Research was approved by the Research Ethics Committee of A.C. Camargo Cancer Center.

Statistical analyses were performed by using SPSS version 20.0 software for Windows (Chicago, IL, USA). Statistical significance was set at $p<0.05$. Descriptive statistical methods were used to compare clinical characteristics of the patients and postoperative complications of NSM. Chi-square or Fisher's exact tests, Student's t-test, and the Mann-Whitney U test were used to evaluate associations between measures. Simple and multiple logistic regression were used to identify significant predictors of developing complications.

RESULTS

A total of 367 NSMs were performed in 290 patients for treatment of breast cancer or for risk-reduction between January 2007 and December 2017 at A.C. Camargo Cancer Center. Of these NSM procedures, 154 (42%) were bilateral, with 74/154 (48%) being prophylactic NSMs, 16/154 (10.4%) being therapeutic, and 64/154 (41.6%) being therapeutic and contralateral prophylactic NSMs (Figure 1).

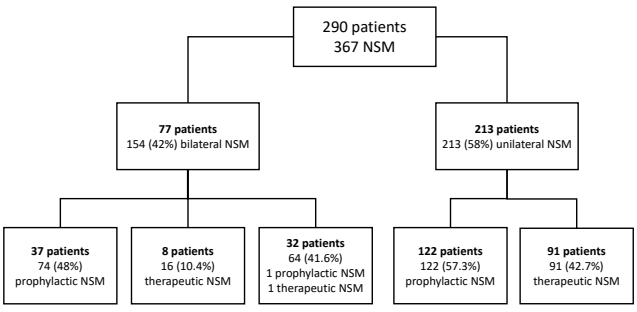

Figure 1. Number of patients and nipple-sparing mastectomies (NSM) performed at A.C. Camargo Cancer Center between January 2007 and December 2017.

The mean age of the cohort examined was 47 years (range 26–74), 29 (10%) were smokers and 43 (14.8%) were former smokers, 35 (12.1%) were obese, and 172 (59.3%) were premenopausal. The most prevalent comorbidities included hypothyroidism (19.3%), systemic arterial hypertension (15.9%), dyslipidemia (9.3%), and diabetes (5.9%) (Supplementary Table 1).

The overall complication rate for the cohort was 40% (n=116). Among the 213 patients who underwent unilateral NSM, 74 (34.7%) developed postoperative complications. Meanwhile, 42/77 (54.5%) patients who underwent bilateral NSM presented postoperative complications. According to indication, postoperative complications were reported for: 32.7% (52/159) of patients undergoing prophylactic NSM, 44.4% (44/99) of patients undergoing therapeutic NSM, and 62.5% (20/32) of patients undergoing simultaneous therapeutic and contralateral prophylactic NSM. Among the 72 patients with a current or previous smoking habit, 44 (61.1%) developed postoperative complications. Among the 35 obese patients, 21 (60%) presented postoperative complications. Breast ptosis was also evaluated, and postoperative complications were observed in 26 (35.6%), 23 (41.1%), and 16 (57.1%) patients exhibiting mild, moderate, and accentuated breast ptosis, respectively. A total of 16 patients had a history of chest wall radiotherapy (RT), with six (37.5%) developing postoperative complications. Finally, among the 75 patients who previously underwent breast surgery, 34 (45.3%) presented postoperative complications. Overall, only bilateral/unilateral NSMs ($p=0.004$), therapeutic and/or prophylactic NSMs ($p=0.004$), and obesity ($p=0.015$) showed statistically significant differences for postoperative complications (Table 1).

A simple logistic regression analysis showed that unilateral NSM was associated with a lower chance of postoperative complications (OR=0.44; 95% confidence interval (95%CI) 0.26–0.75; $p=0.003$), whereas patients who underwent therapeutic and contralateral prophylactic NSM during the same surgery had three times higher chance of developing postoperative complications (OR=3.42; 95%CI 1.55–7.54; $p=0.002$). This association was further corroborated by multiple logistic regressions (OR=3.12; 95%CI 1.09–8.95; $p=0.03$). Both simple and multiple logistic regression analyses also demonstrated that obese patients had a greater chance of developing postoperative complications (OR=2.55; 95%CI 1.24–5.25, $p=0.01$; and OR=3.57; 95%CI 1.33–9.55; $p=0.01$, respectively) (Table 1). When evaluating if age contributed to postoperative complications, the mean age of women who developed postoperative complications *versus* those who did not was not significantly different ($p=0.169$), even when compared according to age groups ($p=0.131$) (Supplementary Table 2).

Complications were categorized as follows: partial or total NAC necrosis (21.7%), partial or total wound dehiscence (21.4%), partial or total skin flap necrosis (14.5%), wound infection

Table 1. Associations between risk factors and postoperative complications in patients who underwent nipple-sparing mastectomy (NSM).

Variables	Complications				Chi-square / Fisher's exact test	Simple logistic regression analysis			Multiple logistic regression analysis		
	No N(%)		Yes N(%)		p	p	OR	95%CI	p	OR	95%CI
Laterality											
Bilateral	35	45.5	42	54.5	0.004*		Ref			Ref	
Unilateral	139	65.3	74	34.7		0.003*	0.44	0.26–0.75	0.449	0.69	0.26–1.78
Indication											
Prophylactic	107	67.3	52	32.7	0.004*		Ref			Ref	
Therapeutic	55	55.6	44	44.4		0.059	1.64	0.98–2.76	0.62	1.18	0.60–2.35
1 Breast prophylactic and 1 Breast therapeutic	12	37.5	20	62.5		0.002*	3.42	1.55–7.54	0.03*	3.12	1.09–8.95
Smoking status											
Non-smoker	136	62.7	81	37.3	0.138		Ref				
Smoker	18	62.1	11	37.9		0.95	1	0.46–2.28			
Former Smoker	20	46.5	23	53.5		0.05	1,9	0.99–3.73			
Obesity											
No	160	63.0	94	37.0	0.015 *		Ref			Ref	
Yes	14	40.0	21	60.0		0.01*	2.55	1.24–5.25	0.01*	3.57	1.33–9.55
Breast ptosis											
No	10	71.4	4	28.6	0.189		Ref				
Mild	47	64.4	26	35.6		0.612	1.38	0.39–4.84			
Moderate	33	58.9	23	41.1		0.394	1.74	0.48–6.24			
Accentuated	12	42.9	16	57.1		0.087	3.33	0.83–13.25			
Previous chest Radiotherapy											
No	164	59.9	110	40.1	1		Ref				
Yes	10	62.5	6	37.5		0.834	0.89	0.31–2.53			
Previous breast surgery											
No	133	61.9	82	38.1	0.338		Ref				
Yes	41	54.7	34	45.3		0.274	1.34	0.79–2.28			

OR: odds ratio; CI: confidence interval; *p<0.05.

(10.3%), and hematoma (7.2%). A total of 38 (13.1%) women needed reoperations. The NAC was excised in 20 (6.9%) cases, 13 (4.5%) due to total necrosis, five (1.7%) due to the presence of invasive carcinoma in the retroareolar margin, and two (0.7%) due to the presence of carcinoma ***in situ*** in the retroareolar margin (Table 2).

The present data demonstrated that bilaterality, simultaneous therapeutic and contralateral prophylactic NSM, and obesity are factors associated with a higher risk of postoperative complications. Comparing to patients who underwent unilateral NSM, those who underwent bilateral NSM presented a greater incidence of skin flap necrosis (26 *vs.* 10.3%, respectively; p=0.002), hematoma (14.3 *vs.* 4.7%, respectively; p=0.012), wound infection (22.1 *vs.* 6.1%, respectively; p=0.0001), and reoperation (22.1% *vs.* 9.9%, respectively; p=0.012) (Table 2). Logistic regression analysis identified unilateral NSM as a protective factor for skin flap necrosis (OR=0.32; 95%CI 0.16–0.64; p=0.001), hematoma (OR=0.29; 95%CI 0.12–0.72; p=0.008), wound infection (OR=0.22; 95%CI 0.10–0.49; p=0.0001), and reoperation (OR=0.38; 95%CI 0.19–0.77; p=0.008) (Table 3).

Table 2. Associations between risk factors and types of postoperative complications in patients who underwent nipple-sparing mastectomy (NSM).

No. patients who underwent NSM	NAC necrosis N%		Skin flap necrosis N%		Hematoma N%		Wound infection N%		Wound dehiscence N%		Reoperation N%		NAC Loss N%	
Overall (n=290)	63	21.7	42	14.5	21	7.2	30	10.3	62	21.4	38	13.1	20	6.9
Laterality	0.803		0.002*		0.012*		0.0001*		0.324		0.012*		0.532	
Bilateral (n=77)	18	23.4	20	26	11	14.3	17	22.1	20	26	17	12.1	7	9.1
Unilateral (n=213)	45	21.1	22	10.3	10	4.7	13	6.1	42	19.7	21	9.9	13	6.1
Indication	0.169		0.011*		0.003*		0.015*		0.435		0.280		0.001*	
Prophylactic (n=159)	28	17.6	17	10.7	5	3.1	14	8.8	30	18.9	20	12.6	3	1.9
Therapeutic (n=99)	26	26.3	15	15.2	10	10.1	8	8.1	23	23.2	11	11.1	12	12.1
1 Breast prophylactic +1 Breast therapeutic (n=32)	9	28.1	10	31.3	6	18.8	8	25	9	28.1	7	21.9	5	15.6
Obesity	0.382		0.217		0.022*		0.139		0.663		0.03*		0.022*	
No (n=254)	52	20.5	34	13.4	14	5.5	23	9	53	20.9	29	11.4	14	5.6
Yes (n=35)	10	28.6	8	22.8	6	17.1	6	17.1	9	25.7	9	25.7	6	17.1

NSM: nipple-sparing mastectomy, NAC: nipple-areola complex. Chi-square/Fisher's exact test *p<0.05.

Table 3. Associations between risk factors and postoperative complications of nipple-sparing mastectomy (NSM).

Risk Factors	Outcome	Simple Logistic Regression Analysis		
		OR	95%CI	p
Therapeutic	Skin flap necrosis	1.49	0.70–3.14	0.293
Prophylactic+therapeutic		3.79	1.54–9.34	0.004*
Unilateral		0.32	0.16–0.64	0.001*
Therapeutic	Hematoma	3.46	1.14–10.44	0.02*
Prophylactic+therapeutic		7.10	2.02–24.99	0.002*
Unilateral		0.29	0.12–0.72	0.008*
Obesity		3.54	1.26–9.94	0.016*
Therapeutic	Wound infection	0.91	0.36–2.25	0.84
Prophylactic+therapeutic		3.45	1.30–9.10	0.012*
Unilateral		0.22	0.10–0.49	0.0001*
Unilateral	Reoperation	0.38	0.19–0.77	0.008*
Obesity		2.68	1.14–6.29	0.023*
Therapeutic	NAC loss	7.17	1.97–26.1	0.003*
Prophylactic+therapeutic		9.63	2.17–42.6	0.003*
Obesity		3.54	1.26–9.94	0.016*

NAC: nipple-areola complex; OR: odds ratio; CI: confidence interval. *p <0.05

Women who underwent simultaneous therapeutic NSM and contralateral prophylactic NSM developed a greater number of complications than those who underwent therapeutic NSM or prophylactic NSM. For these three groups, significant differences in skin flap necrosis (31.3%, 15.2%, and 10.7%, respectively; p=0.011), hematoma (18.8%, 10.1%, and 3.1%, respectively; p=0.003), wound infection (25, 18.8, and 10.1%, respectively; p=0.015), and NAC loss (15.6%, 12.1%, and 1.9%, respectively; p=0.001) were observed (Table 2). Furthermore, patients who underwent therapeutic NSM and contralateral prophylactic NSM during the same surgery had three times higher chance of developing skin flap necrosis (OR=3.79; 95%CI 1.54–9.34; p=0.004) and wound infection

(OR=3.45; 95%CI 1.3–9.1; p=0.012). However, this increased risk was not observed for patients who underwent therapeutic NSM. Regarding hematoma and NAC loss, a higher chance of developing these complications was associated with patients undergoing simultaneous therapeutic and contralateral prophylactic NSM or therapeutic NSM. Compared to women who underwent prophylactic NSM, the chance of developing a hematoma was higher for those who underwent therapeutic NSM (OR=3.46; 95%CI 1.14–10.44; p=0.02), and even higher for women who underwent simultaneous therapeutic NSM and contralateral prophylactic NSM (OR=7.1; 95%CI 2.02–24.99; p=0.002). A similar profile was observed regarding NAC loss, with seven times higher chance observed for patients who underwent therapeutic NSM (OR=7.17; 95%CI 1.9–26.1; p=0.003) and nine times higher chance for patients who underwent simultaneous therapeutic and contralateral prophylactic NSM (OR=9.63; 95%CI 2.1–42.6; p=0.003), compared to patients who underwent prophylactic NSM (Table 3).

Obese patients presented the greatest number of overall complications, although a statistically significant association with obesity was only observed for hematoma (17.1% *vs.* 5.5%, respectively; p=0.02), reoperation rate (25.7% *vs.* 11.4%, respectively; p=0.03), and loss (17.1% *vs.* 5.6%, respectively; p=0.02) (Table 2). Obese patients had three times higher chance of developing hematoma and NAC loss (OR=3.54; 95%CI 1.26–9.94; p=0.016) and two times higher chance of needing reoperation (OR=2.68; 95%CI 1.26–9.94; p=0.016) (Table 3).

Among the 13 patients treated with neoadjuvant chemotherapy (NCT), no postoperative complications were reported (p=0.138). Meanwhile, among 131 patients who underwent therapeutic NSM, 47 (35.9%) received adjuvant treatment with hormone therapy (HT) alone, eight (6%) received radiotherapy alone, three (2.3%) received chemotherapy (CT) alone, 21 (16%) received CT and HT, 17 (13%) received RT, CT, and HT, 14 (10.7%) did not receive any adjuvant treatment, and data for two patients were not available (Supplementary Table 3). Patients who received only adjuvant radiotherapy have been treated with NCT. The start of adjuvant treatment did not significantly differ among the patients who underwent unilateral or bilateral NSM (p=0.078), or among those who underwent therapeutic or simultaneous therapeutic and contralateral prophylactic NSM (p=0.449) (Table 4).

DISCUSSION

An increased demand for specialized breast cancer services has been reported worldwide, after the Angelina Jolie Effect.[14] In addition, studies have shown a trend towards a progressive increase in bilateral risk-reducing NSM and contralateral NSM in patients who have already undergone mastectomy for cancer treatment.[15,16] A recent study has further demonstrated a growth trend in the indication of NSM, not only for risk-reduction, but also for treatment of larger tumors.[17]

Cosmetic contraindications of NSM include factors associated with postoperative complications which impact cosmetic results and the malposition of NAC. Both large breast size and breast ptosis are reported to be absolute cosmetic contraindications of NSM, due to the difficulties associated with managing a large skin envelope.[18] Breasts heavier than 800 g also present two to five times greater chance of developing postoperative complications.[19,20] In the present study, obesity (defined as body mass index (BMI) >30 cm/m^2) was associated with two to three times higher chance of developing postoperative complications. In order to expand NSM indications, reconstruction of large and ptotic breasts can be managed by using a staged approach, with mastopexy or reduction performed prior to NSM in prophylactic surgery candidates.[21]

Increased BMI, diabetes mellitus, smoking, previous breast incisions, prior chest or breast radiotherapy, and NCT have been identified as relative contraindications for NSM.[2,8,10,11,18,20,22] In the present study, no associations between patient's age, smoking status, breast ptosis, prior chest radiotherapy, or prior breast surgery were observed for NSM postoperative complications.

There are few studies which have compared postoperative complications between bilateral and unilateral NSMs, and none of them found statistical differences between laterality and the incidence of postoperative complications.[7,13] In a study conducted by Wang et al., 51 unilateral and 166 bilateral NSMs were compared to 187 unilateral and 394 bilateral Skin-Sparing Mastectomy. Bilateral surgery was found to be associated with a longer hospital stay, yet it was not associated with higher complications rates.[13] In contrast, cases of unilateral NSM examined in the present study were associated with a lower rate of postoperative complications.

Previously, NSM postoperative complication rates have been reported to range up to 53.7%.[7] In the present study, the overall

Table 4. Time to start of chemotherapy and/or adjuvant radiotherapy in patients who underwent unilateral/bilateral therapeutic nipple-sparing mastectomy (NSM) and therapeutic/simultaneous therapeutic and contralateral prophylactic NSM.

Therapeutic NSM	Time to start of adjuvant treatment (months)	Mann-Whitney U test
	Mean ± SD (range)	*p*
Bilateral	2.1 ± 1.48 (0 – 5)	0.078
Unilateral	1.5 ± 1.1 (0 – 4)	
Therapeutic Unilateral	1.64 ± 1.2 (0 – 5)	0.449
1 Breast Prophylactic + 1 Breast Therapeutic	1.8 ± 1.32 (0 – 5)	

NSM: nipple-sparing mastectomy, SD: standard deviation. *$p < 0.05$.

complication rate was 40%, consistent with the published literature. However, the relation between indications of NSM and postoperative complications remains controversial. Mitchell et al. compared 833 therapeutic NSM and 1,102 prophylactic NSM, and found that therapeutic NSM was associated with a greater incidence of flap infections.[3] However, other studies have not found differences between indications (therapeutic/prophylactic) of NSM and postoperative complications.[6,11] To the best of our knowledge, the present study is the first to include a third group for comparison: patients who undergo therapeutic and contralateral prophylactic NSM during the same operation. We observed that this third group presented a greater number of postoperative complications, followed by therapeutic NSM alone and prophylactic NSM alone. We also observed that patients who underwent therapeutic and contralateral prophylactic NSM presented three-fold greater chance of experiencing postoperative complications.

NAC necrosis is a significantly adverse postoperative complication of NSM. Rates of NAC necrosis have been reported to range from 0.8%–29.6%.[2,4-11,13,16,17,20,23,24] However, not all cases of NAC necrosis require operation and NAC excision. Wagner et al. reported rates of NAC necrosis up to 29.6%,[10] although most of these cases involved partial NAC necrosis (20.3%) and only 7.4% of the cases required NAC excision.[7] Similarly, Garcia-Etienne et al. described a NAC necrosis rate of 48%, yet only 5% of these cases were removed due to total NAC necrosis.[25] In the present study, NAC desquamation was grouped with partial and total necrosis, resulting in a NAC necrosis rate of 21.7%. However, only 4.5% of the NACs needed to be excised due to total NAC necrosis. Smoking and obesity have also been described as risk factors for NAC necrosis.[10,26] In the present study, NAC necrosis was not found to be related to these or other factors.

Skin flap necrosis is another relatively common postoperative complication of NSM, with incidence rates ranging from 1.5%–37.5%.[2,4,6-11,23]. Just like NAC necrosis, not all cases of skin flap necrosis require surgical debridement. In the present study, partial and total skin flap necrosis were grouped, resulting in a skin flap necrosis rate of 14.5%. Factors reported to be associated to skin flap necrosis in NSM are prior breast surgery, prior breast radiotherapy, duration of surgery, sharp dissection, and specimen size.[10,27] In the present study, neither prior breast surgery nor prior breast radiotherapy were identified as risk factors. However, women who underwent therapeutic and contralateral prophylactic NSM had three-fold higher chance of developing skin flap necrosis. In contrast, women who underwent unilateral NSM had a 68% lower chance of developing skin flap necrosis.

Wound dehiscence rates after NSM have been reported to range from 1.9%–7.7%.[7,10,13,23] In the present study, wound dehiscence rate was 21.4%. This higher rate may be due to our consideration of any wound dehiscence when calculating this rate, not only those which required a second operation. Besides that, no risk factors associated with a higher risk of wound dehiscence were identified.

Regarding hematoma as a postoperative complication of NSM, we observed that patients who underwent unilateral NSM had a 71% lower chance for developing this complication. Furthermore, we observed that patients who underwent therapeutic NSM had three-fold higher chance of presenting hematoma, whereas patients undergoing therapeutic and contralateral prophylactic NSM during the same surgery increased the chance to seven-fold. To the best of our knowledge, we believe the present study is the first to demonstrate an association between laterality and indication (prophylactic/therapeutic) of NSM with hematoma. All patients who underwent NSM received the same thromboembolic prophylaxis.

Two studies have investigated an association between wound infection and indication of NSM. Whereas Spear et al. did not find differences between postoperative infections and therapeutic or prophylactic NSM,[6], Mitchell et al. showed a higher infection rate after therapeutic NSM.[3] In the present study, patients who underwent therapeutic and contralateral prophylactic NSM during the same surgery had a three-fold higher chance of wound infection. Conversely, unilateral NSM was found to be associated with a 78% lower chance of developing postoperative infection.

Reoperation rates of NSM to treat postoperative complications are reported to range from 4.2%–9.4%.[8,13,17] The overall reoperation rate in the present study was 13.1%. Excluding patients who underwent reoperation to excise NAC due to involvement of the retroareolar margin with carcinoma, the reoperation rate found in this study to treat postoperative complications was 10.7%, which is close to the rates reported in other studies.[8,13,17] We further observed that obese patients had two-fold higher chance of reoperation after NSM.

A delay in the start of adjuvant treatment of up to two months after surgery proved to be related to a worse overall survival (OS) in patients with disease stage III, triple-negative and HER2 positive tumors, and a worse disease-free survival (DFS) in patients with disease stage III.[28] Worse OS and DFS have also been reported for patients who received adjuvant radiotherapy 2.3 months and 3 months after surgery, respectively.[29] Riba et al. showed that patients older than 70 years old, with hospital readmission within 30 days after surgery, positive margins after conservative breast surgery, reconstruction with autologous flap, and mastectomy were factors associated with a beginning of adjuvant treatment three months after surgery. In this study, bilateral mastectomy was not associated with a greater chance of delaying systemic treatment;[30] patients who underwent bilateral NSM, therapeutic NSM, or simultaneous therapeutic and contralateral prophylactic NSM, despite having higher risks of postoperative complications, did not have a delay in adjuvant treatment.

Type of breast reconstruction, operative time, and type of dissection (sharp or electrocautery) were not evaluated and consist a limitation of this study. However, our results can be used to discuss with patients which moment is the best to perform the prophylactic NSM.

CONCLUSIONS

We conclude that therapeutic and contralateral prophylactic NSM performed in the same surgery is associated with more postoperative complications, mainly skin flap necrosis, hematoma, wound infection, and NAC loss. Obesity was also observed to be associated with an increased risk of hematoma, reoperation, and NAC loss. Despite major postoperative complications, we observed that laterality (bilateral/ unilateral) and purpose (prophylactic/therapeutic) were not associated with delay in starting adjuvant treatment. When analyzed together, these results suggest that performing therapeutic NSM and contralateral prophylactic NSM at different times as separate procedures could minimize the incidence of postoperative complications, especially for obese patients.

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AUTHORS' CONTRIBUTIONS

M.S.: conceptualization, investigation, methodology, project administration, data curation, writing original draft, writing – review & editing; E.B.: formal analysis, visualization, writing – review & editing; A.K.D.: visualization, writing – review & editing; H.I.: writing – review & editing; F.B.A.M.: conceptualization, formal analysis, investigation, methodology, validation, writing – review & editing.

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ORIGINAL ARTICLE
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Clinicopathologic profile of breast cancer patients treated with neoadjuvant chemotherapy at HUCFF/UFRJ

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ABSTRACT

Introduction: The objective of this study is to describe the profile of patients from a public institution, submitted to neoadjuvant chemotherapy (NACT), comparing the verified pathological response with literature data. **Methods:** Observational retrospective cohort study on breast cancer patients diagnosed between September 2001 and October 2018 and treated with NACT at Hospital Universitário Clementino Fraga Filho (HUCFF/UFRJ), located in Rio de Janeiro, Brazil. The adopted neoadjuvant chemotherapy regimen was based on anthracycline and docetaxel. **Results:** A total of 133 patients were evaluated. The average age in this group was 54 years (28-86), 49 women (37%) were under 50 years old. The following distribution by molecular subtype was observed: overexpression or amplification of the human epidermal growth factor receptor 2 (HER2+) (13 women, 26.6%), Luminal (19 women, 38.8%), and Triple-negative (TN) (17 women, 34.6%). The HER2+ and TN subtypes had a higher incidence of cases between 40-49 years and 50-59 years. As for the initial staging, 34% were IIIA; 26%, IIB; and 19%, IIIB. Only one patient did not undergo surgery after NACT, 33 (24.8%) underwent conservative surgery, and 99 patients (74.4%) underwent mastectomy. Regarding the axillary approach, 41 (31%) underwent sentinel lymph node biopsy and 88 (66%) had an indication for lymphadenectomy. In the anatomopathological evaluation of the surgery, 12 (9.1%) patients obtained a pathologic complete response (pCR) and 113 (84.9%), partial or no response to chemotherapy. **Conclusion:** This research enabled the identification of clinicopathologic characteristics and outcome of patients who received neoadjuvant chemotherapy in a public university service. The predominance of advanced tumors was observed, stressing the need for public health policies for the screening of breast cancer as well as the guarantee of timely treatment for diagnosed cases. The data somewhat reflect the difficulty that the public sector encounters to carry out the most appropriate treatment. The authors expect that this article, by analyzing the profile and the adopted treatment in real-life cases and in a public university institution, can contribute to the improvement of breast cancer treatment in Brazil.

KEYWORDS: locally advanced breast cancer, neoadjuvant chemotherapy, pathological response.

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide. In Brazil, 66,280 new cases of breast cancer are expected per year for the 2020-2022 triennium. This value corresponds to an estimated risk of 61.61 new cases per 100 thousand women[1].

The prognosis of breast cancer depends, among other data, on its extension (staging) and the molecular subtype. TNM (T – tumor; N – nearby lymph nodes; M – metastasis) is the international system for assessing the extent of neoplasia, whose last systematic review was carried out in January 2018 by the American Joint Committee On Cancer (AJCC); this is the 8th edition, incorporating biological factors into the anatomo-clinical data[2]. Pathological staging (pTNM) is determined after surgery or neoadjuvant treatment (ypTNM), with greater accuracy than the clinical one (cTNM).

Neoadjuvant chemotherapy (NACT) was initially adopted for locally advanced tumors aiming at cytoreduction, in order to provide conservative surgeries to patients who are candidates for mastectomy or to make it operable. However, lately, NACT has been adopted with the purpose of evaluating the response to a new protocol or medication, taking advantage of the pathological response as an intermediate outcome, identifying predictive and

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prognostic factors or indicating complementary adjuvant treatment according to the residual disease. The effectiveness of the NACT regimen can be assessed by the rate of objective clinical response, tumor reduction and operability or, preferably, by the pathologic complete response (pCR – absence of residual invasive tumor in the surgical specimen in the breast and axilla). The first studies based on anthracyclines showed rates of clinical responses (60% to 80%) and pCR (10% to 20%)[3,4]. In the early 2000s, taxanes were incorporated into neoadjuvant breast cancer treatment regimens, either alone or combined with anthracyclines, doubling the rate of clinical and pathological response[5-9]. Randomized studies on amplified HER2 (human epidermal growth factor receptor 2) patients have shown a significant increase in pCR when combining chemotherapy with anti-HER2 therapy[10-12]. pCR is the best indicator of response to neoadjuvant treatment, indicating an increase in survival (overall survival and disease-free survival), as initially demonstrated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18 study[13]. This correlation is especially true for triple-negative (TN) and HER2-positive[14] (HER2+) tumors.

The indications and protocols for neoadjuvant therapy in breast cancer are well established in the literature. Nevertheless, in Brazil, we find barriers, mainly in the public sector, due to the delay in diagnosis, the difficulty of infrastructure, and the incorporation of medicines. This study aims to analyze the profile and clinicopathological outcome (pathological response) of patients treated with neoadjuvant therapy, in a clinical oncology service at a university hospital in Rio de Janeiro, Brazil.

MATERIAL AND METHODS

Methodology

This is a retrospective observational cohort study, whose unit of analysis consisted in breast cancer cases diagnosed between 2001 and 2018 and treated with NACT at Hospital Universitário Clementino Fraga Filho/Universidade Federal do Rio de Janeiro (HUCFF/UFRJ), located in the city of Rio de Janeiro, state of Rio de Janeiro, Brazil. The patients included in the study were selected from the HUCFF/UFRJ hospital-based cancer registries. Clinical and pathological data were obtained by consulting physical and electronic medical records.

To assess tumor characteristics, we used the TNM Classification of the Union for International Cancer Control (UICC), 8th edition, considering the size of the tumor – T, the presence of axillary metastasis – N, and the presence of metastasis – M (locoregional or systemic), at the time of diagnosis (cTNM).

The subclassification of breast tumors by immunohistochemistry was performed based on results presented by the Pathological Anatomy of HUCFF/UFRJ based on the evaluation of hormone receptors for estrogen (ER) and progesterone (PR), overexpression of c-erb2, or amplification of the human epidermal growth factor receptor 2 (HER2), and cell proliferation index (Ki67). According to these results, three immunohistochemical subgroups were defined: Luminal subtypes (ER+ and/or PR+/- and HER2-), HER2+ (c-erb2 3+ or 2+, confirmed by FISH [Fluorescence *in situ* hybridization] amplification test), and hormone receptor-positive or negative (HR+/-) and TN or basal-like (ER-, PR-, and HER2-). There is some controversy on the evaluation of Ki67 in the literature due to the difficulty in standardizing its results in different services. The 2011 St. Gallen Consensus considers values below 14% as low or negative and values above 15% as high. However, due to lack of inputs, some patients did not perform the Ki67 evaluation, and they cannot be properly classified into Luminal A and B. Ki67 was described, when possible, to demonstrate tumor aggressiveness.

All patients underwent routine exams for staging and exclusion of metastases before primary chemotherapy. The adopted chemotherapy treatment was the PACS 01 regimen[15], which uses three cycles of FEC (5 fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 with an interval of 21 days) followed by three cycles of docetaxel 100 mg/m^2 every 21 days. Trastuzumab, despite being incorporated into the Brazilian Unified Health System (SUS) since 2013, has not been associated with neoadjuvant chemotherapy in amplified HER2 patients due to logistical difficulties, delay in carrying out the FISH test, and unavailability of the drug to start the treatment (distribution centralized by the Brazilian Ministry of Health with delivery around three months after scheduling the patient). Trastuzumab was administered to these patients in adjuvant therapy for 12 months.

Data from surgical treatment on the breast (conservative or radical procedure) and axilla (lymphadenectomy or sentinel lymph node biopsy) were analyzed. The response to NACT was described as: pathologic complete response (pCR), in the absence of invasive neoplasia in the breast and lymph nodes, in which there may be ductal carcinoma *in situ* (DCIS) in the specimen or partial response in the existence of residual invasive tumor in the breast or lymph node.

Inclusion criteria

Female patients with infiltrating breast carcinoma treated at HUCFF/UFRJ between 2001 and 2018, with neoadjuvant chemotherapy based on anthracyclines and/or taxanes, were eligible for this study.

Exclusion criteria

Patients who abandoned chemotherapy treatment were excluded.

Statistical analysis

The results of this study are exploratory and descriptive. Analyses of quantitative variables are presented with the mean and standard

deviation; the qualitative variables are presented with their absolute and relative frequency. No statistical analysis was performed between the variables due to the small number of cases.

RESULTS

A total of 133 patients treated at HUCFF/UFRJ, diagnosed with breast cancer, and who underwent NACT followed by surgery from September 2001 to October 2018 were evaluated. The distribution of clinical characteristics according to breast cancer subtypes classified by immunohistochemistry is demonstrated in Table 1.

Regarding the age distribution at diagnosis, the average age in this group was 54 years (28–86), with no significant difference between the subgroups HER2+ 54 years old (32–86), Luminal 54 years old (28–86), and TN 52 years old (33–81). In this sample, 49 women (37%) were under 50 years old with the following distribution by molecular subtype: HER2+ (13 women, 26.6%), Luminal subtypes (19 women, 38.8%), and TN (17 women, 34.6%). The distribution by molecular subtype for 10 patients aged 70 years or older was: 5 (50%) Luminal subtypes; 4 (40%), HER2+; and 1 (10%), TN.

As for the HER2+ subgroup, 25 cases were diagnosed with 3+ in immunohistochemistry, whereas eight cases needed to perform the FISH test to confirm the diagnosis. When evaluating the Ki67 cell proliferation marker, a large percentage (69.6%) was found, which is deemed a high cell proliferation index (>14), and 10 cases did not perform the test.

In the Luminal subgroup, 52 cases were classified as HER2 negative (0 and 1+), whereas six cases were c-erbB-2 2+ and required FISH test to be performed. In the evaluation of ER and PR, the following were verified: ER+/PR+=45, ER+/PR-=10, and RPx=3.

Concerning TN, 40 cases were classified as HER2 negative (c-erbB-2 0 and 1+), whereas two cases were c-erbB-2 2+ and required FISH test to be performed. In this population, no cases of low Ki67 were found.

At the time of diagnosis, 71% of the cases had a >5-cm tumor, and in 70% of the cases the armpits were clinically compromised. Almost half of the cases (43%) were classified as staging IIIA; 26%, as IIB; and 19%, as IIIB. Fifteen patients were classified into stage I and IIA, stages in which patients are not usually submitted to neoadjuvant therapy. However, all these patients were initially evaluated by the services of mastology and clinical oncology, and opted for starting treatment with chemotherapy due to the rapid clinical evolution and structural difficulties. Subsequently, it was verified that 10 of these patients had subtypes TN and amplified HER2. See Table 1.

After receiving NACT, patients were referred to surgical evaluation, with only one patient considered inoperable. Table 2 shows that conservative surgery was an infrequent practice, and only 33 patients (25%) underwent such a procedure. Other 99 patients (74%) had an indication for radical surgery. Concerning axillary surgery, a total of 41 patients (31%) underwent sentinel lymph node biopsy (11 HER2 women, 17 Luminal, and 13 TN) and 88 patients (66%) had an indication for lymphadenectomy (21 HER2 women, 39 Luminal, and 28 TN). In this sample, seven cases (5%) did not undergo an axillary evaluation.

In the anatomopathological evaluation of post-NACT surgery, 12 patients (9%) obtained pCR (4 HER2 women, 2 Luminal, and 6 TN). In 113 (85%) patients, there was partial or no response to chemotherapy (26 HER2 women, 54 Luminal, and 33 TN).

Table 1. Distribution of clinical characteristics according to breast cancer subtypes.

	Total (%)	HER2 (%)	Luminal subtypes (%)	TN (%)
Age at diagnosis				
20–29	1 (1)	0 (0)	1 (100)	0 (0)
30–39	14 (10)	3 (21)	6 (42)	5 (37)
40–49	34 (26)	10 (30)	12 (35)	12 (35)
50–59	43 (32)	9 (21)	19 (44)	15 (35)
60–69	28 (21)	6 (21)	14 (50)	8 (29)
70–79	10 (7)	4 (40)	5 (50)	1 (10)
80–89	3 (3)	1 (33)	1 (33)	1 (33)
Tumor size				
cT1	2 (1)	1 (50)	1 (50)	0
cT2	37 (28)	12 (32)	16 (43)	9 (25)
cT3	66 (50)	15 (23)	24 (36)	27 (41)
cT4	28 (21)	5 (18)	17 (61)	6 (21)
Lymph node evaluation				
cN0	40 (30)	12 (30)	17 (42)	11 (28)
cN1	62 (47)	13 (21)	25 (40)	24 (39)
cN2	29 (22)	7 (24)	15 (52)	7 (24)
cN3	2 (1)	1 (50)	1 (50)	0 (0)
Distant metastasis				
M0	133 (97)	33 (25)	58 (43)	42 (32)
M1	0 (0)	0 (0)	0 (0)	0 (0)
Clinical Staging				
I	2 (1)	1 (50)	1 (50)	0 (0)
IIA	13 (10)	8 (62)	3 (23)	2 (15)
IIB	34 (26)	4 (12)	19 (56)	11 (32)
IIIA	57 (43)	15 (26)	17 (30)	25 (44)
IIIB	25 (19)	4 (16)	17 (68)	4 (16)
IIIC	2 (1)	1 (50)	1 (50)	0 (0)
TOTAL	133	33	58	42

HER2: human epidermal growth factor receptor 2; TN: triple-negative; cT: clinical stage of the tumor; cN: clinical stage of nearby lymph nodes; M: metastasis.

Table 2. Surgical treatment of the breast and axilla.

	Total (%)	HER2 (%)	Luminal subtypes (%)	TN (%)
Surgical treatment of the breast				
Conservative surgery	33 (25)	10 (30)	12 (36)	11 (34)
Radical surgery	99 (74)	22 (22)	46 (46)	31 (32)
Not performed	1 (1)	1 (100)	0 (0)	0 (0)
Surgical treatment of the axilla				
Sentinel lymph node biopsy	41 (31)	11 (27)	17 (41)	13 (32)
Lymphadenectomy	88 (66)	21 (24)	39 (44)	28 (32)
Not performed	4 (3)	1 (25)	2 (50)	1 (25)
Histopathology of the axilla (SL and lymphadenectomy)				
Negative lymph node	52 (39)	15 (29)	16 (31)	21 (40)
Positive lymph node	74 (56)	17 (23)	38 (51)	19 (26)
Not evaluated	7 (5)	1 (14)	4 (57)	2 (29)
TOTAL	133	33	58	42
Pathologic complete response – pCR				
Yes	12 (9)	4 (33)	2 (17)	6 (50)
No	113 (85)	26 (23)	54 (48)	33 (29)
Not evaluated	8 (6)	3 (37)	2 (26)	3 (37)
TOTAL	133	33	58	42

HER2: human epidermal growth factor receptor 2; TN: triple-negative; SL: sentinel lymph node; pCR: pathologic complete response.

DISCUSSION

Locally advanced breast cancer remains an important public health issue in Brazil. About 32% of breast cancer patients diagnosed at the National Cancer Institute have locally advanced disease[16]. This study evaluates this universe of patients, reporting their profile, adopted treatment, and obtained results.

Patients treated at HUCFF from 2001 to 2018 who underwent NACT were selected for the analysis. The patients had a mean age of 54 years (28–86) and 49 women (37%) were under 50 years old. These data are similar to those described in a Brazilian observational study that included 4,912 patients, conducted in 28 public and private healthcare centers, and described an average age of 54 years and 44.3% of patients under 50 years of age[17]. According to the guidelines of the Brazilian Ministry of Health, this population would not be subjected to screening tests[18].

At the time of diagnosis, 71% of cases had a >5-cm tumor, and 70% had a clinically compromised axilla. Almost half of the cases (43%) were classified as staging IIIA, followed by 26% IIB, and 19% IIIB, with NACT being adopted with purpose of operability and to increase conservative surgical procedures. These findings demonstrate the delay in diagnosis, probably caused by the difficulty of access to screening tests and delay in diagnosis in the public sector. These findings are similar to those described in another oncological center of national reference[19].

According to the immunohistochemical profile, a predominance of aggressive HER2+ (26.6%) and TN (34.6%) subtypes were observed, which differ from the normal distribution of the population with breast cancer described in other Brazilian series, according to which the Luminal subtypes predominate with 57.9%; overexpression of HER2 with 17.6%; and triple-negative with 24.2%[20]. This fact can be justified by the selection of locally advanced breast cancer patients.

This is a retrospective study, conducted over a long period of time (17 years). This fact could arise a methodological difficulty due to changes in the protocols considered. Nevertheless, due to the difficulty in technological incorporation, there was no major change in the adopted regimen of neoadjuvant therapy.

A 9% pCR was observed, which is well below the value currently reported in the international literature, but compatible with the report of other Brazilian series[21,22]. HER2+ tumors were not treated with neoadjuvant trastuzumab achieving a 12% response, whereas in the literature on dual inhibitor, a response of up to 60% was obtained[11,12]. Thus, these patients shall also present a lower response of overall and disease-free survival, as pCR has been confirmed as an intermediate marker capable of predicting survival[23].

Currently, the evaluation of the residual tumor according to the methodology suggested by M. D. Anderson is considered the most employed method in the literature[24]. However, considering that this is a long-term retrospective study, with difficulties in obtaining and reviewing the anatomopathological tests of the surgical specimens, the pathologic complete response was considered as the absence of an invasive tumor in the breast and lymph nodes.

Although the pCR is lower than that reported in the literature, most patients obtained a partial response and almost all patients were able to perform the surgery (99%). In 21 patients (15.7%), it was possible to perform conservative surgery and search for sentinel lymph nodes, avoiding axillary dissection. Unfortunately, the actual assessment of axillary downstaging was difficult to document, as patients did not perform histopathological or cytological analysis of the pre-NACT lymph node. Of 93 patients (69.9%) with clinically palpable axillary lymph nodes, at the beginning of the study, 52 (39%) had a negative axilla according to the histopathological examination.

HER2-positive patients (positive FISH or IHC [immunohistochemistry] 3+) have a proven benefit of combined chemotherapy treatment with anti-HER2 therapy. Studies evaluating the role of adding trastuzumab to chemotherapy have shown increased pCR and increased survival[10]. Subsequently, new inhibitors of the HER2 pathway, such as lapatinib, tyrosine kinase inhibitor

(NEO-ALTO)[11], and pertuzumab (NeoSphere)[12], were tested alone and combined with chemotherapy, and showed a pCR benefit in relation to HER2 dual inhibitor. Thus, most international guidelines recommend the use of trastuzumab and pertuzumab, preferably in an anthracycline-free regimen, to avoid cardiotoxicity[25,26] as a neoadjuvant therapy for patients with HER2-positive tumors greater than 2 cm[27].

In TN and HER2 amplified patients, NACT has been early indicated, in tumors larger than 1 cm and 2 cm respectively, or positive axilla, as these tumors are quite aggressive and have good response to chemotherapy. In addition, the adoption of NACT to these patients is intended to guide adjuvant treatment, as recent randomized and prospective studies demonstrate the benefit of survival with the use of capecitabine in TN[28] and Trastuzumab emtansine (T-DM1) in HER2[29] in patients with residual disease.

The standard treatment of neoadjuvant chemotherapy for TN patients remains anthracyclines and taxanes, with the still controversial addition of platinum, antiangiogenic therapy, poly (ADP-ribose) polymerase inhibitors (PARP), and immunotherapy[30,31].

Neoadjuvant chemotherapy based on anthracyclines and taxanes remains the standard therapy adopted in SUS. Trastuzumab was approved by SUS in 2013 for use in initial breast cancer, in adjuvant and neoadjuvant treatments. However, to date, its use has not been adequately incorporated due to difficulties in the immunohistochemistry test of HER2 or in the acquisition of the drug.

CONCLUSION

This research enabled the identification of clinicopathologic characteristics and outcome of patients who received neoadjuvant chemotherapy in a public university service. A predominance of tumors larger than 5.0 cm and positive axilla was verified, reinforcing the need for public health policies aimed at consolidating the national breast cancer screening program as well as ensuring timely treatment for diagnosed cases.

The data somewhat reflect the difficulty that the public sector encounters to perform the appropriate treatment or that recommended by international guidelines. The authors expect that this article, by analyzing the profile and the adopted treatment, in real cases and in a public university institution, can contribute to the improvement of breast cancer treatment in Brazil.

AUTHORS' CONTRIBUTION

L.C.B.A.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing – original draft, writing – review & editing; M.F.D.G.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing – original draft, writing – review & editing; A.H.P.C.C.: formal analysis, supervision, visualization, writing – review & editing; N.H.S.C.: formal analysis, supervision, visualization, writing – review & editing

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ORIGINAL ARTICLE
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Comparative analysis: QOL in breast cancer patients before and during the COVID-19 pandemic

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ABSTRACT

Introduction: The 2019 outbreak of coronavirus disease (COVID-19) posed unprecedented challenges of emotional matter for women diagnosed with breast cancer. This research aimed to compare the quality of life of patients who were diagnosed with breast cancer from 2014 to 2019, and patients who were diagnosed during the COVID-19 pandemic, from January to August 2020. **Methods:** A cross-sectional study was performed, including patients with breast cancer, associated or not with chronic pathologies, with no psychiatric disorders, aged over 18 years. The questionnaire developed by the European Organisation for Research and Treatment of Cancer (EORTC-C30) version 3.0 was used for the comparative analysis of quality of life. The study population consisted of 185 women, of which 43.2% (n = 80) were previously diagnosed and 56.7% (n = 105) were diagnosed during the pandemic, with a median age of 45 years (IQ = 15). **Results:** The EORTC-C30 quality of life score remained the same for both groups (33.33; 33.33). There was a decrease in the scores on the emotional (58; 50) and physical (60; 40) scales of patients diagnosed during the pandemic. **Conclusions:** Future longitudinal research should contribute to the understanding of the long-term effects of COVID-19 on the psychological health of patients with breast cancer.

KEYWORDS: breast neoplasms; coronavirus infections; quality of life.

INTRODUCTION

Cancer is considered one of the main causes of death worldwide, and, among the female population, the breast tumor is the most prevalent in Brazil and in the world[1]. According to the literature, approximately 50% of cancer patients suffer from psychiatric disorders, in such a way that anxiety and depression are generally considered to be the most important and prevalent psychopathological comorbidities[2]. This psychological morbidity is caused by changes in physical appearance after treatment, limitations in physical functioning and daily activities, limited functioning in previous roles, and the stigma of the disease, which compromise the patient's quality of life[3].

All the emotional overload due to a cancer diagnosis was enhanced by the coronavirus pandemic (Sars-CoV-2) and the resulting disease, COVID-19, which emerged in December 2019. Initial reports suggested that patients with a history of or active malignancy may be at increased risk of contracting the disease and developing complications related to COVID-19, as it is an immunocompromised group due to the effects of antineoplastic therapy and supportive drugs, in addition to the immunosuppressive properties of cancer itself[4,5].

Among factors related to the outcome of breast cancer, the quality of life of patients is an important parameter, considering that it influences the prognosis of the disease and can be used to manage the condition and treatment of the patient, assist in taking medical decisions, control symptoms, and plan supportive care interventions[6]. Although previous studies address the issue of COVID-19 and cancer patients, the literature does not present studies that assess the quality of life of patients diagnosed with breast cancer during the pandemic. This study aimed to compare the quality of life of patients who were diagnosed between 2014 and 2019 and of patients who were diagnosed during the COVID-19 pandemic from January to August 2020.

MATERIAL AND METHODS

Study design

A cross-sectional and epidemiological study was developed for analyzing data on the periods from 2014 to 2019, and from January to August 2020, provided by participants of the *Centro de Apoio ao Paciente com Câncer de Londrina* [Londrina Cancer

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Support Center] (state of Paraná, Brazil) and by patients of the *Centro de Tratamento Oncológico Pro Onco* [Pro Onco Oncological Treatment Center].

Study population

The study population included a convenience sampling consisting of 185 women who were diagnosed with breast cancer and underwent treatment between 2014 and August 2020. The eligibility criteria included patients with breast neoplasms associated or not with chronic pathologies, with no psychiatric alterations, aged over 18 years. Patients who underwent treatment prior to 2014 were excluded from the research. The interviews took place remotely, through telephone calls or an online questionnaire. In both instruments, the participants were asked to answer a questionnaire with objective questions. The Informed Consent Form was sent by a message application for signature before starting the study.

Study questionnaire

Questions from the questionnaire developed by the European Organisation for Research and Treatment of Cancer (EORTC-C30) version 3.0 were used to assess the quality of life of patients during the treatment of breast cancer. The EORTC-C30 is a multidimensional and self-administered questionnaire for patients with breast, esophageal, or lung cancer that includes a total of 30 questions addressing 5 functional scales (role, physical, emotional, social, and cognitive), 1 scale on overall quality of life, in addition to 3 symptom scales (fatigue, pain, and nausea/vomiting) and 6 additional items related to other symptoms (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial impact). A final question was added to the EORTC-C30 for patients who underwent treatment during the year 2020 to assess the psychological impact of the pandemic on these women.

Ethical aspects

This study was carried out after approval by the Research Ethics Committee 35791720.0.0000.0020 by means of the participants' signed consent, after a detailed explanation of its development, in accordance with resolution No. 466/2012 of the National Health Council and the Declaration of Helsinki.

Statistical analysis

For data analysis, the Statistical Package for the Social Sciences (SPSS) program, version 22.0, was used, and the adopted level of significance was 5%. Data distribution was determined by Kolmogorov-Smirnov and Shapiro-Wilk tests. The median and interquartile range were used to indicate measures of central tendency and dispersion. Variables were submitted to Spearman's correlation analysis and were presented as correlation index and p-value. The EORTC-C30 Scoring Manual was used to calculate the medians of the questionnaire domains, which were transformed into a linear scale from 0 to 100 points. The interpretation of the manual scores implies that the score of zero is related to a worse health condition, whereas the score of 100 represents patients with better functioning levels. The exception is for the scoring of the symptom scales, in which the highest score represents the worst symptomatology.

RESULTS

From August to October 2020, 185 women were interviewed. The group diagnosed before the pandemic corresponds to n = 80 patients, and the group diagnosed during the pandemic corresponds to n = 105 patients. Table 1 shows the patients' sociodemographic data. The median age of the patients was 45 years (IQ = 15). Among them, 54% of the patients (n = 100) were white, 37.8% (n = 70) were black, and only 8.1% (n = 15) were Asian. Regarding marital status, 49% of patients (n = 92) were married, 34% (n = 63) were divorced, 10.81% (n = 20) were widows, and only 5.4% (n = 10) were single.

The clinical characteristics related to the treatment are shown in Table 2. Of the total sample, 95.13% of patients (n = 169) underwent surgery, 91.35% (n = 176) underwent chemotherapy, and 65.40% (n = 121) underwent radiotherapy. However, most patients underwent more than one treatment modality, which justifies the overlapping percentage.

Table 1. Sociodemographic data and clinical characteristics of patients.

	n = 185 (%)
Age	Median = 45 years (IQ = 15)
Ethnicity	
White	100 (54)
Black	70 (37.8)
Asian	15 (8.1)
Religion	
Have a religion	163 (88.1)
Have no religion	22 (11.8)
Marital status	
Married	92 (49)
Single	10 (5.4)
Divorced	63 (34)
Widow	20 (10.81)

Table 2. Clinical characteristics of patients.

Type of treatment	n (%)
Chemotherapy	169 (91.35)
Radiotherapy	121 (65.40)
Surgery	176 (95.13)

Table 3 shows the median and interquartile range of the scales and symptoms addressed in the EORTC-C30. Although the median quality of life remained the same for both groups (33.33), the results show that patients diagnosed during the pandemic had the lowest physical scale median (40) in relation to the patients diagnosed before the pandemic (60). In addition, the emotional scale of the group diagnosed during the pandemic was lower (50) than that of patients diagnosed before the pandemic (58).

To assess whether the pandemic influenced the quality of life of patients with breast cancer, Spearman's correlation analysis between the questionnaire variables was performed. The correlation analysis showed that there was no relationship with changes in quality of life among women treated before or during the pandemic (r = -0.016; p = 0.83). Nevertheless, there was a weak association between the treatment period and the patients' emotional function (r = -0.146; p = 0.047), demonstrating that the pandemic had a negative impact on the patients' emotional status. Chemotherapy is related to 11 of the 13 aspects analyzed by the EORTC-C30, which shows a worsening of the symptoms of women undergoing this treatment (Table 4).

Table 3. Median and interquartile range of the items of the functions and symptoms of the questionnaires of the European Organisation for Research and Treatment of Cancer.

Items	Period	Median	Interquartile range
Functions*			
Physical	Before the pandemic	60.00	60.00
	During the pandemic	40.00	60.00
Emotional	Before the pandemic	58.30	41.70
	During the pandemic	50.00	33.30
Cognitive	Before the pandemic	50.00	66.67
	During the pandemic	50.00	33.33
Financial impact	Before the pandemic	00.00	66.67
	During the pandemic	33.33	66.67
Role	Before the pandemic	50.00	100.00
	During the pandemic	50.00	37.50
Social	Before the pandemic	66.67	50.00
	During the pandemic	66.67	50.00
Quality of life	Before the pandemic	33.33	33.33
	During the pandemic	33.33	33.33
Symptoms**			
Insomnia	Before the pandemic	66.67	50.00
	During the pandemic	33.33	33.33
Loss of appetite	Before the pandemic	33.33	66.67
	During the pandemic	33.33	58.33
Constipation	Before the pandemic	33.33	66.67
	During the pandemic	33.33	66.67
Diarrhea	Before the pandemic	00.00	33.33
	During the pandemic	16.67	33.33
Fatigue	Before the pandemic	44.44	44.44
	During the pandemic	44.44	41.67
Pain	Before the pandemic	66.67	50.00
	During the pandemic	66.67	50.00
Nausea/ vomiting	Before the pandemic	83.33	50.00
	During the pandemic	66.67	50.00

*The closer to one hundred, the better the Overall Quality of Life; **The closer to zero, the worse the Overall Quality of Life.

DISCUSSION

In this study, between January and August 2020, the impact of breast cancer diagnosis on the patients' quality of life, before the pandemic (2014–2019) and during the new coronavirus pandemic (from January to August 2020), was compared. Although the assessment of quality of life was the same in both groups, as it is a sample of young patients (median = 45 years), the literature pinpoints that women under 50 years of age are more likely to have a lower quality of life because they are in a very active age group, in which they need to reconcile motherhood, their occupation, and loving and social relationships, in comparison with older women[7]. Thus, age is directly related to greater concerns regarding self-image, sexuality, menopause, and loss of fertility[8], which justifies the low score in the quality of life of both groups (33.33).

Previous studies have also associated faith and spirituality, characteristics of the Brazilian culture, as coping mechanisms that act in the perception of quality of life[9]. In addition to the age group and cultural aspects, another factor associated with quality of life and reported during the interviews is the disease itself, which requires distancing measures and hygiene care similar to those imposed by the pandemic, due to the immunosuppressive properties of cancer and the antineoplastic therapy[4,5]. Thus, the limitations that the group diagnosed during the pandemic encountered did not differ from the restrictions experienced by previously diagnosed and treated patients.

Nevertheless, the analysis demonstrates a worsening in the emotional state of the patients who were diagnosed during the year 2020. Previous studies report that the population with breast cancer is at high risk of developing emotional disorders due to the disturbing nature of the diagnosis, treatments, and long-term adverse effects[10]. In addition to the already known risks, the result is also related to the fear of contracting the virus (Sars-CoV-2) and the subsequent impact on treatment, besides the concern with access to oncology services during the pandemic. As a result, patients carry the emotional burden of doubt about whether their treatments will be delayed and what would be the implications for their outcome. In addition to these uncertainties, there are measures of social distancing and the limitations of

Table 4. Correlations between the scales of the European Organisation for Research and Treatment of Cancer and quality of life, treatment period, and therapeutic modalities.

	Treatment period	QOL	Chemotherapy	Radiotherapy	Surgery
Physical					
Spearman	-0.032	-0.250**	-0.057	-0.145	-0.105
p	0.669	0.001*	0.43	0.04*	0.15
Emotional					
Spearman	-0.146	-0.049	-0.114	-0.123	-0.073
p	0.04*	0.504	0.124	0.095	0.324
Loss of appetite					
Spearman	–0.028	0.119	0.184*	0.177*	0.221**
p	0.701	0.106	0.012*	0.016*	0.002*
Dyspnea					
Spearman	0.007	0.148*	0.232	0.154*	0.015
p	0.925	0.044*	0.001*	0.036*	0.836
Insomnia					
Spearman	-0.117	0.011	0.173*	0.121	0.027
p	0.114	0.879	0.019*	0.101	0.714
Constipation					
Spearman	0.134	0.178*	0.190**	0.095	-0.090
p	0.069#	0.015*	0.010*	0.200	0.222
Diarrhea					
Spearman	0.067	-0.060	0.141	0.166*	0.060
p	0.363	0.420	0.056*	0.024	0.417
Role					
Spearman	-0.044	-0.152*	-0.203**	-0.195**	-0.033
p	0.553	0.039*	0.006*	0.008	0.654
Cognitive					
Spearman	0.038	-0.150*	-0.240**	-0.046	0.046
p	0.605	0.041*	0.001*	0.532	0.539
Social					
Spearman	-0.142	-0.175*	-0.229**	-0.193**	0.054
p	0.054	0.017*	0.002*	0.009*	0.468
Fatigue					
Spearman	0.062	-0.192**	-0.240**	-0.284**	-0.065
p	0.398	0.009*	0.001*	0.000*	0.376
Pain					
Spearman	0.040	-0.108	-0.150*	-0.293**	-0.079
p	0.592	0.142	0.041*	0.000*	0.286
Nausea/vomiting					
Spearman	-0.009	-0.167*	-0.262**	-0.160*	-0.090
p	0.906	0.023*	0.000	0.030*	0.224
Quality of life					
Spearman	-0.016	1.000	0.125	-0.154*	-0.027
p	0.831	-	0.089	0.037	0.717

*Significant results ($p < 0.05$); **Significant results ($p < 0.01$); #Tendency toward significance.

visitors, which weakens opportunities for family support, affecting an important sense of connection and a source of strength for patients with breast cancer[11].

There was also a deterioration in the physical scale of patients treated during the pandemic. A meta-analysis provided evidence that programs of physical exercises performed during or after breast cancer treatment have a small, but positive impact on physical functioning and cancer-related fatigue in patients with breast cancer compared with conventional care[12]. However, the transmissibility of COVID-19 is greater in sports environments due to the viability of the virus as well as its incubation period and milder symptomatology[13]. The fear of being exposed to physical exercise outside their house and the consequent decrease in physical activity during the pandemic may be related to the worsening of the patients' physical scale.

The correlation analysis showed that chemotherapy significantly affects the domains analyzed by the EORTC-C30. This finding corroborates previous studies that point to chemotherapy as an emotional drainage experience, which can affect patients for a long time after the end of treatment. Patients who underwent chemotherapy may experience prolonged fatigue for up to three years after treatment[14]. Nonetheless, it is unclear whether the lower index of quality of life in patients who underwent chemotherapy is caused by the treatment itself or by a more aggressive neoplasm or a more advanced stage compared with those who did not need to undergo chemotherapy[7].

Although previous studies have pointed out the social isolation resulting from the pandemic as an adverse factor in the mental health of patients[15], some women considered quarantine to be a beneficial period, as they were able to keep the diagnosis and treatment of cancer confidential. Therefore, because they did not need to be exposed to work environments and social events, the patients reported feeling preserved from the concern and curiosity of others.

The present study has limitations. Due to social distancing, participants were recruited by means of a message application and by telephone calls, therefore, they may not be fully representative of the population with breast cancer in general. Furthermore, the study lacks information about socioeconomic data and possible comorbidities associated with breast cancer. Finally, individual differences between cancer patients and survivors play an important role in quality of life and present themselves as a limitation, considering that this perception is shaped by some personality traits, and not only by physical, sociodemographic, and oncological variables[16].

CONCLUSION

Although the quality of life score remained the same in both groups, the results demonstrated that women who were diagnosed during the pandemic had a lower physical and emotional score compared with previously diagnosed patients. Further research should continue to monitor the long-term effects of COVID-19 on the psychological health and quality of life of patients with breast cancer.

AUTHORS' CONTRIBUTIONS:

A.C.S.A.H.: Conceptualization, data curation, methodology, investigation, project administration, resources, supervision, validation, writing – review & editing.

L.A.P.: Conceptualization, investigation, data curation, formal analysis, methodology, investigation, resources, visualization, writing – original draft.

M.C.S.P: Conceptualization, investigation, data curation, formal analysis, methodology, investigation, resources, visualization, writing – original draft.

C.E.C.: Supervision, data curation, validation, software, writing – review & editing.

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Burow's triangle advancement flap: a reliable tool on oncoplastic breast-conserving surgery

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ABSTRACT

Oncoplastic techniques in breast cancer treatment allow increasing indications of breast-conserving surgery and improving cosmetic results. Breast tumors located at the superior edge of the upper quadrant or at the upper inner quadrant represent a challenge for conservative surgery due to insufficient breast thickness and risk of skin involvement. We present a modified Burow's triangle advancement flap for breast-conserving surgery in patients with breast tumors at these locations. This retrospective observational study analyzed 8 out of 213 patients submitted to major oncoplastic breast procedures, who underwent breast-conserving surgery with matrix rotation mammaplasty, using a modified Burow's triangle advancement flap. All patients were treated in public and private health systems in Santiago, Chile. The median age at diagnosis was 47 years. The average initial tumor size was 5.9 cm, and the mean excised breast weight was 117 g. Patients required neither symmetrization nor displacement of the nipple-areola complex. Only one patient had a minor complication (wound dehiscence). During follow-up, no local recurrences were reported. We conclude that the modified Burow's triangle advancement flap is a safe and effective technique to manage tumors at this complex location. It provides adequate oncological margins, good cosmetic results, and contralateral symmetry, with complication rates similar to those of standard conservative surgery.

KEYWORDS: breast neoplasms; surgical flaps; mastectomy, segmental; mammaplasty.

INTRODUCTION

Breast-conserving surgery (BCS) including axillary treatment and radiotherapy has become the standard of care for most breast cancer patients, reaching long-term survival rates similar to those of radical mastectomy[1,2]. However, in many cases, the cosmetic results are unsatisfactory given the percentage of breast volume to be resected or its location, leading to severe breast deformities, skin retraction, nipple-areola complex (NAC) distortion or deviation, and secondary contralateral breast asymmetry. Oncoplastic breast surgery (OBS) techniques were developed to offer an advantage over classical breast-conserving treatment in selected patients. OBS allows larger breast resection for cancer treatment with minimal deformities, larger free resection margins, and lower re-excision rates while maintaining equivalent oncological outcomes[3,4]. According to a recently published volumetrically-based OBS classification system, volume displacement or replacement techniques can be used depending on the proportion of breast volume resected[5]; for all of them, including different types of reduction mammaplasty with large breast reshaping, local advancement flaps have been described whenever the defect cannot be covered with the same breast[6-10].

Even with many oncoplastic techniques, some patients will still need a total mastectomy to obtain satisfactory cosmetic or adequate oncological results. Tumors located at the superior edge of the upper quadrant or at the upper inner quadrant usually replace the whole breast thickness, compromising the anterior margin and making it difficult to preserve the skin. Tumors at these locations are a challenge for conservative surgery, whenever necessary to resect the entire breast thickness, as it might produce secondary glandular deformity, high risk of positive tumor margins, and upper NAC deviation[11].

We present a modified triangular advancement flap for breast cancer to preserve the breast in difficult cases.

The present study aimed to assess the reliability and safety of Burow's triangular advancement flap. This technique, usually described

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for the correction of facial defects[12-18], can be applied to the breast so as to preserve it in difficult cases, with minimal effect on breast volume and mostly without need of contralateral breast symmetrization.

METHODS

This retrospective observational study analyzed a prospectively maintained database cohort of female patients with breast cancer diagnosed at the Breast Surgical Unit of San Borja Arriarán Clinical Hospital and private practices in Santiago, Chile, between August 2010 and November 2019. In the study period, 213 patients were treated with conservative surgery and major oncoplastic procedures. Among them, eight patients were diagnosed with tumors located at the high upper quadrant or at the upper inner quadrant. They were treated with BCS, using the triangular resection described below. The same senior breast surgeon, who was fully trained in oncologic and reconstructive breast surgery, performed both procedures and followed up the patients.

Descriptive statistics was carried out to analyze the results.

Selection criteria

All patients were diagnosed with breast cancer and managed by a multidisciplinary breast cancer team. They were submitted to conventional preoperative exams and had a previous percutaneous biopsy, with histological and immunohistochemical (IHC) analysis for hormone receptor status, HER2, and Ki67. Clinical evaluation was performed to determine the location of the tumor in the breast, distance to the skin, possible multicentricity, and potential axillary involvement. Patients fulfilling the inclusion criteria had tumors located closer than 16 cm from the sternal notch and/or less than 7 cm from the sternal midline.

Imaging studies included mammogram, ultrasound, computed tomography (CT) scan, and bone scan to identify local and distant involvement. The indication for primary conservative surgery was based on the tumor/breast ratio and IHC results. Patients with cT3 tumors received neoadjuvant chemotherapy. Other factors were taken into account for surgical planning, such as previous breast surgery that could hinder adequate local blood supply for advancement glandular flaps. Associated risk factors for local complications, such as diabetes, active smoking, and obesity, were recorded. Furthermore, contralateral breast shape was considered when evaluating the need for symmetrization surgery.

Surgical technique

Skin markings were made on patients in a standing position right before surgery. The inframammary fold, sternal midline, breast boundaries, and tumor location were marked. The nipple position was not changed. A curved line with inferior concavity was drawn from the mid-axillary line with the arm abducted 90º, extending medially parallel to the clavicle, 1–2 cm above the tumor location in the breast. Next, a triangle was drawn with the upper base in this line. The base width depended on the tumor size and should have at least 1 cm of macroscopic safe surgical margins. The triangle vertex was drawn long down in relation to the lateral margin of the tumor toward the NAC in order to achieve posterior orderly and harmonic breast rotation without deformity of central breast projection. At the axillary region, a small upside-down triangle (Burow's triangle) was drawn to enable access to the axilla for either sentinel lymph node biopsy or axillary dissection, which later allowed skin compensation when the rotation advancement dermoglandular flap was done (Figure 1).

Under general anesthesia, a triangular incision was performed, with resection of the main triangle, including the whole breast thickness, the tumor, its overlaid skin, and the pectoral fascia. Histologic tumor margins were assessed by a pathologist contemporarily. Free margins were defined as no tumor cells at the inked margin of the specimen for invasive carcinoma and a 2 mm margin for ductal carcinoma *in situ*[19]. Tumor bed was marked with vascular clips. A simultaneous axillary study was carried out through the small triangular resection drawn before. The curved line incision was completed between both triangles straight to the pectoralis major muscle. Afterward, this lateral dermoglandular flap was raised from the muscle just enough to allow its advancement toward the medial border of the main triangle resected before (Figure 2). Accurate hemostasis was performed. If necessary, closed-suction drains were placed on the breast and axilla. The advancement flap was closed in 2 layers with 2-0 interrupted absorbable Vicryl® sutures (Vicryl®: Ethicon, J&J), 3-0 subcutaneous Vicryl®, and 3-0 or 4-0 absorbable monofilament (Monocryl®; Ethicon, J&J). Wounds were dressed with gauze. Patients were discharged the day after surgery. Drains were removed 2–7 days after surgery.

Postoperative assessment

Weekly clinical examinations were performed until the final histology was received. Oncological treatments were completed according to national protocols, with chemotherapy, radiotherapy, biological treatment, and hormonal blockade if needed.

Cosmetic evaluation

Cosmetic outcomes were assessed using photographic documentation of each patient taken preoperatively and 6–12 months post-surgery and radiotherapy. Seven surgeons independently analyzed each case and classified them into excellent, good, fair, or poor, according to the Harris Scale[20].

RESULTS

The median patient age at diagnosis was 47 years (range 26–71). The mean body mass index (BMI) was 25 (range 21–29). All patients were symptomatic at diagnosis (palpable tumor). Histological reports showed seven invasive ductal and one invasive lobular carcinoma. The IHC analysis revealed five luminal, one luminal

HER2+, and two triple-negative breast cancers. At diagnosis, one patient had stage I cancer, three patients had stage II, and four had stage III. The mean initial clinical tumor size was 5.9 cm (range 3–13). Three patients received neoadjuvant chemotherapy, one with pathological complete response, one with pathological partial response, and the last one with initial clinical response, but having a secondary progression during chemotherapy, forcing us to advance the surgery before completing neoadjuvant chemotherapy (Figure 3). No patient required contralateral breast symmetrization. The mean resected tumor size was 2.9 cm (range 0–7). The mean resected specimen weight was 117 g (range 53–257). All patients had adequate histological margins on final pathologic reports, and none required re-excision surgery before adjuvant radiotherapy. According to the Harris scale, the cosmetic result was considered excellent in 28.6% of cases, good in 51.8%, fair in 16.1%, and poor in 3.5%. No major complications were reported. One patient had minor wound dehiscence, requiring only outpatient management. Median follow-up was 59 months (range 1–129). To date, no patient has had local recurrence. A patient developed contralateral breast cancer 48 months after the first diagnosis and was diagnosed with distant metastasis at 93 months of follow-up. Among these patients, no deaths have been reported (Table 1).

DISCUSSION

Oncoplastic surgery increases the indication for BCS in case of large tumors or tumors at difficult locations of the breast, making it possible to obtain better cosmetic results and adequate surgical margins[1,2,7,10]. Tumors located at the upper quadrants can be excised and repaired by different oncoplastic techniques, including glandular reshaping or undermining, inferior pedicle mammaplasty[21], round-block[22], racket resection[7,23], batwing technique[24], among others. The main issues of all these techniques are repositioning the areola at the center of the new breast and avoiding a filling defect due to insufficient tissue after reshaping. However, in some areas, repairing partial mastectomy defects is extremely difficult, like in the site known as "no man's land"[25], which refers to tumors located closer than 16 cm from the sternal notch and/or less than 7 cm from the sternal midline.

Tumors in this area usually leave a significant filling defect, especially if the skin section must be excised. The solution comes with volume replacement techniques, such as the latissimus dorsi flap[26] and the more recently described immediate fat grafting, which shows promising results[27].

The application of Burow's triangle advancement flap — first described in the early 19th century[12] for facial defects — to the breast[11,28] has become a fast and straightforward technique, allowing resecting the whole thickness of the affected breast quadrant, including its skin, and partial breast reconstruction with a volume displacement approach involving lateral dermoglandular rotation and advancement flap. Burow's triangle corresponds to a compensatory excision of redundant tissue at the proximal edge of any advancement flap in order to improve cosmesis and avoid standing cones[14]. The size of the Burow's triangle can be reduced by extending the length of the flap, especially useful when resecting breast tumors at the "no man's land

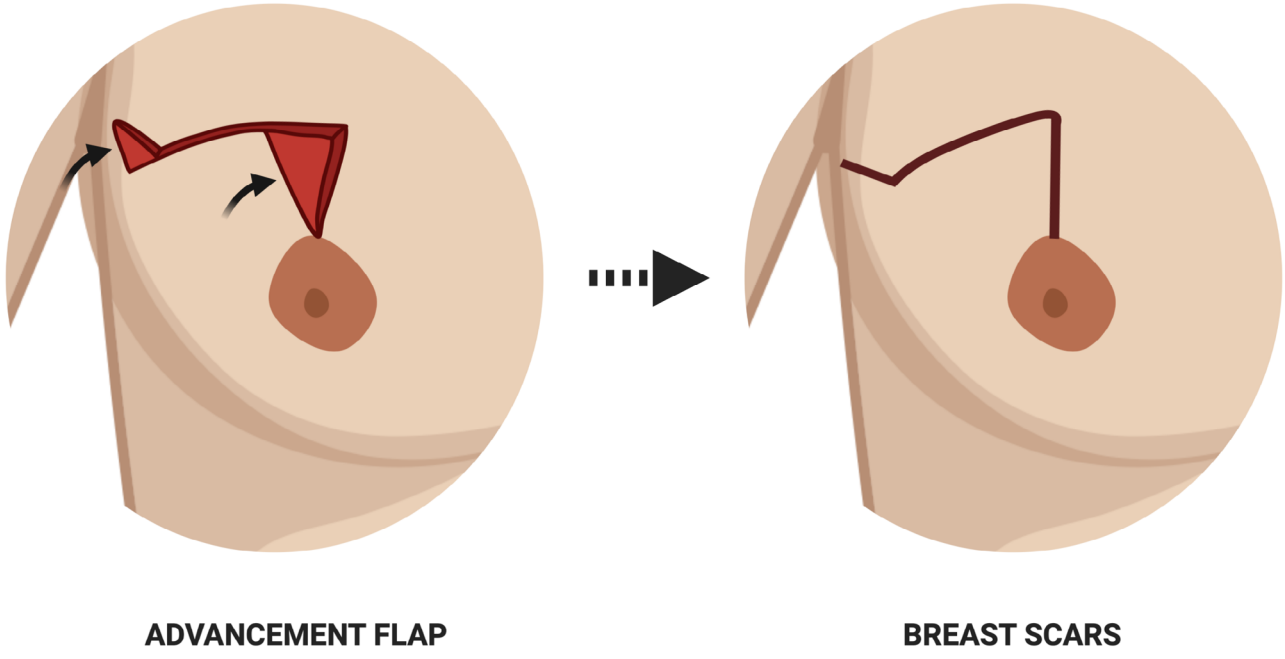

Figure 1. Schema of breast advancement flap after a triangular resection and a small upside-down "Burow" triangle to allow skin compensation in the axillary region.

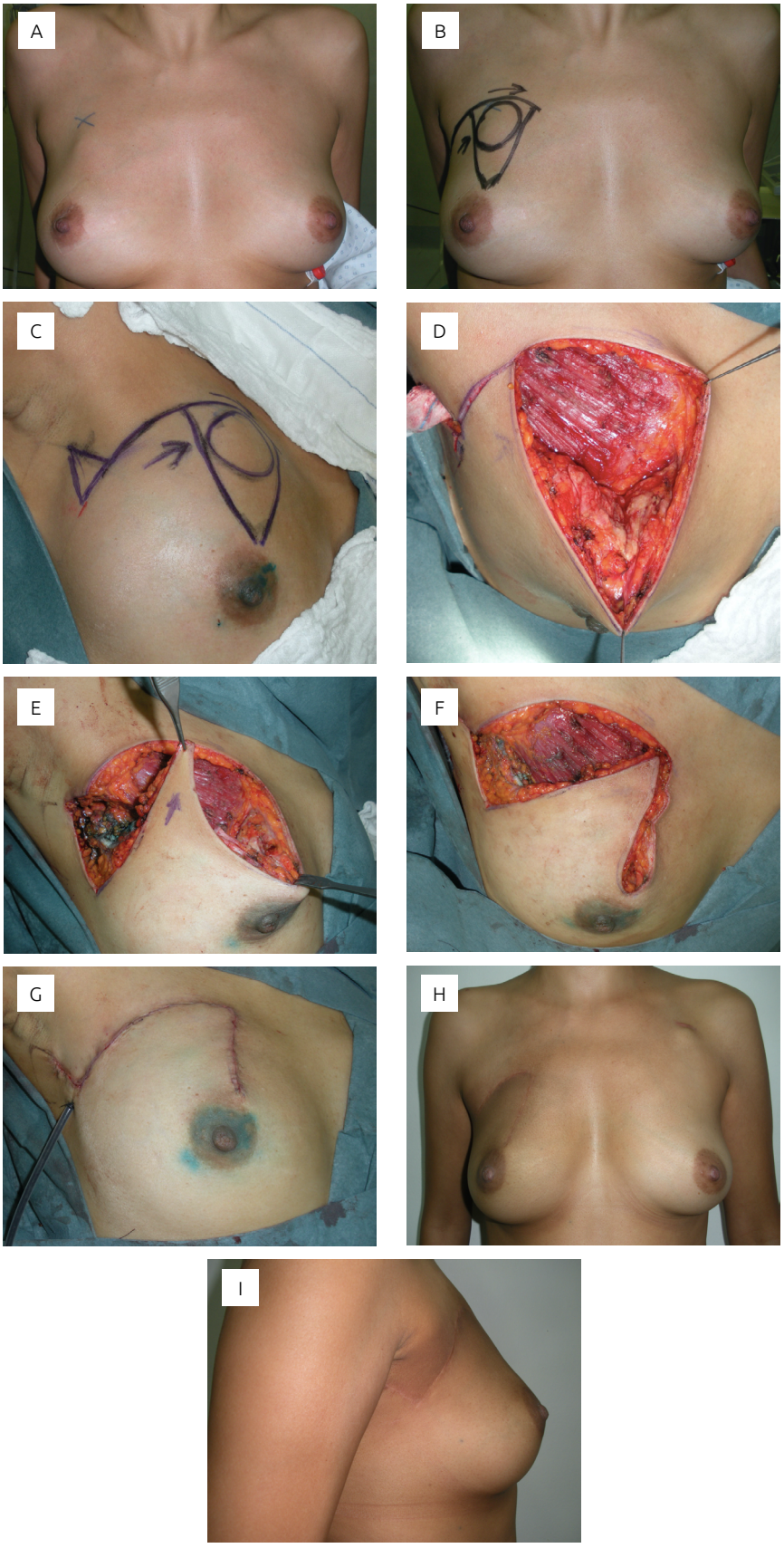

Figure 2. 37-year-old patient. 3.5-cm luminal A invasive ductal carcinoma, located 10 cm from the sternal notch. Triangular quadrantectomy (90 g) with negative SLNB* (A–D). Lateral glandular matrix rotation to cover the breast defect (E–G). 4-year follow-up pictures (H and I) with symmetrical breast shape and scars that tend to fade after radiotherapy.
*SLNB: sentinel lymph node biopsy.

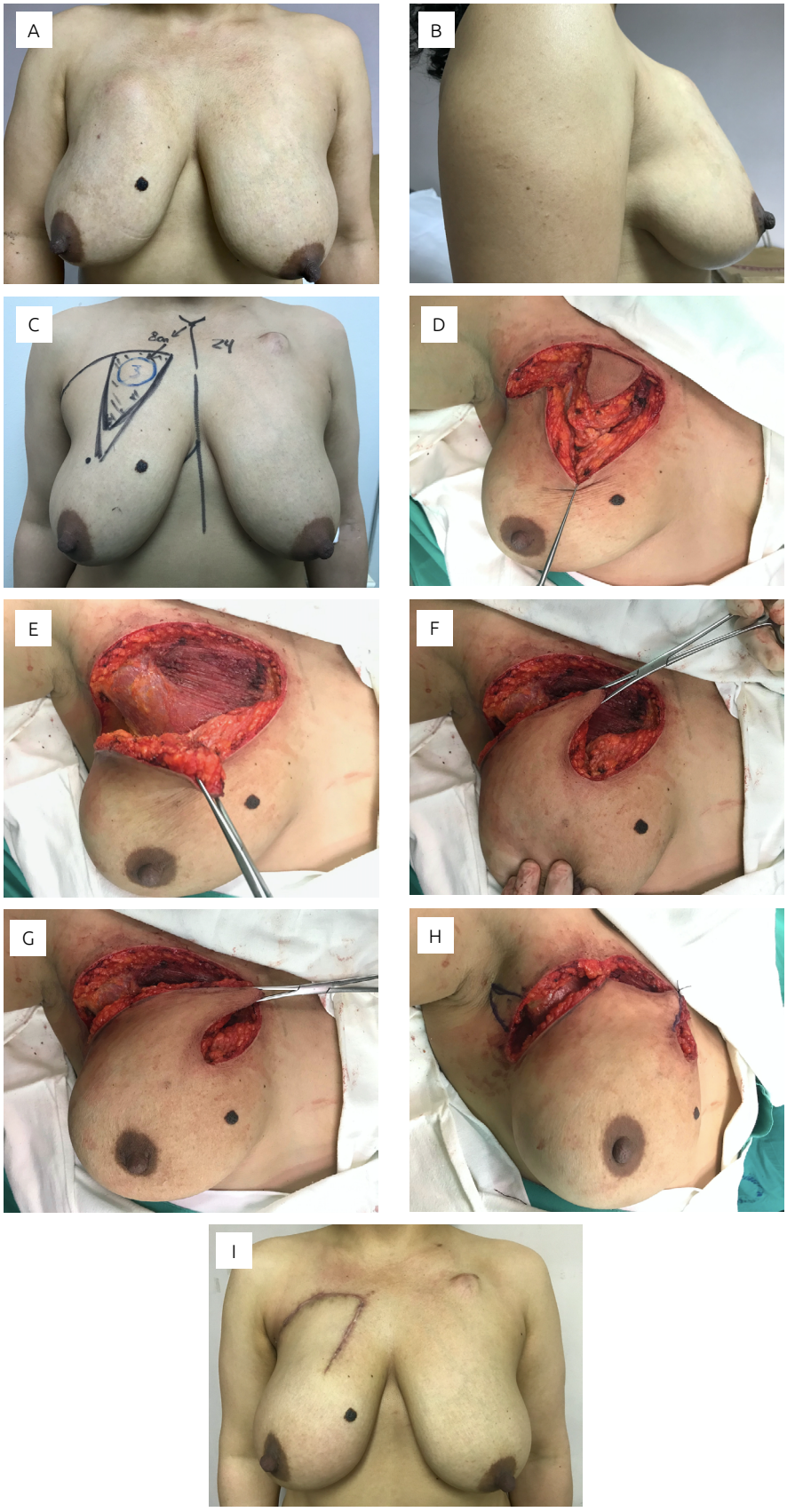

Figure 3. 34-year-old patient. 5-cm triple-negative invasive ductal carcinoma (IDC). (A, B) T3N2M0 neoadjuvant chemotherapy with adequate response to anthracycline regimen but progression with taxanes. (C–E) Large breast resection, including skin and a superficial layer of the pectoral muscle (65 g). Pathology report: 2.5-cm IDC, Elston III. Axillary dissection: 17 negative lymph nodes. (F–H) Lateral glandular matrix rotation. (I) 3-month follow-up pictures with acceptably symmetrical breast shape.

area" and when access to the axilla is necessary. The advantages of this flap include a wide, well-vascularized pedicle and the ability to place the compensatory triangle relatively far from the oncological defect, allowing good access to the axilla[14-18]. If the flap is judiciously planned, the breast shape can be preserved without major NAC displacement. Operative time does not increase significantly from a standard BCS. Since symmetrization surgery is not required, a second surgical team is not needed. The complication rate is low. In our cohort, only one partial wound dehiscence was described, requiring outpatient treatment. A disadvantage of this technique is the large scar, sometimes in a visible area; however, the cosmetic result was excellent or good in most patients, according to the postoperative photographic evaluation (80.4%). No patient required conversion to total mastectomy. This could be explained by the adequate preoperative breast assessment with images, the careful management of margins during surgery, and the concept that oncoplastic techniques are associated with lower incidence of positive margins and secondary reoperations[29,30,31].

By applying the oncoplastic partial breast reshaping technique described herein, we can avoid converting these surgeries to total mastectomy and posterior breast reconstruction, reducing the high postoperative complication rate associated with breast reconstruction and posterior radiotherapy[32]. This technique allows performing wider excisions and, therefore, obtaining adequate surgical margins. The local breast recurrence rate should be as low or even lower than that of conventional partial mastectomy[29,30]. In our cohort, only one patient developed contralateral breast cancer and distant metastasis, but, to date, none of them has had any local recurrence, showing the safety of this technique[33].

Table 1. Characteristics of patients who underwent breast surgery with modified Burow's triangle technique (N=8).

Median age (year, range)	47 (26–71)
Mean initial tumor size (cm, range)	5.9 (3–13)
Mean pathological size (cm, range)	2.9 (0–7)
Mean excised breast volume (g, range)	117 (53–257)*
Mean BMI (range)	25 (21–29)
Histological type (core biopsy)	
Invasive ductal carcinoma	7
Invasive lobular carcinoma	1
Molecular subtype (according to IHC)	
Luminal	5
Luminal HER2+	1
Triple-negative	2
Stage at diagnosis	
Stage 0 (*in situ*)	0
Stage I	1
Stage II	3
Stage III	4
Stage IV	0
Median follow-up (range, months)	59 (1–129)
Local recurrence	0
Distant metastasis	1
Contralateral new breast cancer	1

*One patient had a pathological complete response after neoadjuvant chemotherapy, corresponding to the 0 value in range; BMI: body mass index; IHC: immunohistochemical analysis.

CONCLUSION

Local breast advancement flaps are an essential part of partial breast reconstruction tools, with which every breast surgeon should be familiar. The Burow's triangle advancement flap offers significant benefits, such as a straightforward and fast coverage of upper inner surgical breast defects. This flap allows an excellent matching of skin color, texture, thickness, shape, volume, and sensibility regarding the original breast and very close similarity to the contralateral one, often avoiding the need for a symmetrization surgery. The compensatory triangle can be hidden in the axillary region. Its main disadvantage is the evident geometrical scar outside the esthetic landmarks of the breast, which must be understood and accepted by the patient. Fortunately, most of the time, the scars partially fade after radiotherapy.

Modified Burow's triangle advancement flap is a technique that can be safely used in breast surgery, with adequate oncological and cosmetic outcomes, avoiding total mastectomy and giving more patients the opportunity to have a BCS.

AUTHORS' CONTRIBUTIONS

J.L.: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review & editing.
M.R.: Data curation, formal analysis, investigation, methodology, validation, surgical technique, visualization, writing – review & editing.
C.R.: Conceptualization, validation, visualization, writing – original draft, writing – review & editing.
A.B.: Validation, visualization, writing – original draft, writing – review & editing.
G.I.: Validation, visualization, writing – original draft, writing – review & editing.
D.H.: Validation, visualization, writing – original draft, writing– review & editing.
J.G.: Validation, visualization, writing – original draft, writing – review & editing.

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ORIGINAL ARTICLE
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Evaluation of clinical and pathological response factors to neoadjuvant chemotherapy in breast cancer patients

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ABSTRACT

Objectives: To evaluate breast cancer (BC) patients treated with neoadjuvant chemotherapy (NACT) and to analyze clinicopathological features correlating with pathological complete response (PCR) and survival outcomes. **Methods:** Observational, descriptive, and retrospective study. The medical records of BC patients who underwent NACT were reviewed and analyzed using the Statistical Package for the Social Sciences (SPSS), version 20.0. **Results:** Of the 176 BC patints who underwent NACT, 62 patients (35.2%) achieved PCR. The PCR rate was 22% (n = 2) for luminal A, 15% (n = 9) for luminal B/HER2-negative, 45.5% (n = 15) for luminal B/HER2-positive, 50% (n = 14) for non-luminal/HER2-positive, and 47.8% (n = 22) for triple-negative (p = 0.01). Histological grade, estrogen receptor (ER) expression, progesterone receptor (PR) expression, and HER2 status were significantly associated with PCR (p = 0.022, p = 0.01, p = 0.01, and p = 0.02, respectively). The median follow-up was 35.9 months, the estimated 5-year disease-free survival (DFS) was 96.7% in the PCR group and 83.2% in the non-PCR group (p = 0.05). The estimated 5-year overall survival (OS) was 95.5% in the PCR group and 69.1% in the non-PCR group (p = 0.017). Overall, 11 patients (6.25%) presented with locoregional recurrence (LRR), one (1.6%) in the PCR group and 10 (8.8%) in the non-PCR group (p = 0.10). **Conclusion:** We observed higher PCR rates in triple-negative and HER2-positive molecular subtypes. DFS and OS were significantly better in patients who achieved PCR, regardless of clinicopathological features. We also observed lower rates of LRR in the population that reached PCR.

KEYWORDS: breast neoplasms; neoadjuvant therapy; molecular biology; residual volume.

INTRODUCTION

Breast cancer (BC) is a heterogeneous and complex disease[1]. During the last decade, genomic analyzes using microarrays have revolutionized the field of BC research[2]. Molecular subtypes were identified, outlining different risk factors[3,4], different prognoses[5], as well as different natural histories, different survival rates and sensitivity to local and systemic treatments[6-9].

Neoadjuvant chemotherapy (NACT) is equivalent in overall survival (OS) compared to adjuvant chemotherapy in the treatment of BC. Unlike adjuvant treatment, NACT has traditionally been relegated to patients with locally advanced, initially inoperable BC. However, NACT has played an increasingly important role in the treatment of early-stage disease[10]. NACT has benefits in several clinical strategies, including tumor size reduction and remission of the involvement of the axillary lymph nodes by metastases (downstaging), aiming at a less mutilating surgery, with breast preservation and with resection only of the sentinel lymph nodes in case of negative axillary lymph nodes.

One of the main benefits of NACT is the prognostic information obtained by the pathological evaluation of the tumor bed and axillary lymph nodes after surgery. The complete pathological response is strongly associated with a better prognosis of patients undergoing NACT, as observed in clinical trials NSABP B-18 and B-27[11,12].

Given the arguments presented, we believe that it is extremely important to analyze our population of patients with BC who underwent NACT and understand the subpopulation of responders and non-responders to conventional treatments, as well as to assess survival outcomes.

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METHODS

All the medical records of patients who underwent NACT with a diagnosis of breast malignancy, between March 2012 and June 2020, in the oncology service (UNACON) of the General Hospital (HG) in Caxias do Sul and in the clinic practice were reviewed. The study included all patients who received NACT diagnosis through anatomopathological examination of invasive carcinoma, selecting cases of both non-special invasive breast carcinomas and special breast carcinomas, with histological grades from I to III and with stages from I to IIIC. Data were recorded on forms, as shown in Appendix 1.

The status of estrogen receptor (ER)/progesterone receptor (RP), epidermal growth factor receptor 2 (HER2) protein, and Ki-67 antigen with the following primary antibodies were assessed: monoclonal antibody (MAb) to ER (Dako , clone EP1, prediluted), MAb to RP (Dako, clone PgR, prediluted), MIB-1 MAb to Ki-67 antigen (Dako, clone MIB-1, prediluted) and polyclonal antiserum (Biogen, clone SP3, 1/1,100 dilution) in HER2 protein. Intense and complete membrane staining in at least 10% of tumor cells was qualified for immunohistochemical expression (IHC) of HER2 3+ and considered to be HER2 positive. For this analysis, HER2 scores of 0 and 1+ were considered negative. All HER 2+ tumors were tested for gene amplification by fluorescence in situ hybridization (FISH). The Ki-67 labeling index value was divided into low (< 14%) and high (≥ 14%). Tumors were stratified into subtypes[13]:

- luminal A: ER positive and/or PR positive, HER2 negative, and low Ki-67 (< 14%);
- luminal B/HER2 negative: ER positive, PR positive, HER2-negative, and Ki-67 high (≥ 14%);
- luminal B/HER2 positive: ER positive, PR positive, HER2 positive, and any Ki-67;
- non-luminal/HER2 positive: ER negative, PR negative, and HER2 positive;
- triple negative: ER negative, PR negative, and HER2 negative.
- Pathologic complete response (PCR) was defined as the absence of invasive carcinoma in the breast and ipsilateral axilla after NACT[14].

Regarding the post-NACT pathological evaluation, the pieces were duly evaluated according to well-established international recommendations[15]. The piece was weighed and measured and the surgical margins were painted with India ink; subsequently, 0.5 cm slices were cut from anterosuperior to posterior inferior and each slice was labeled as 1, 2, 3, etc. and subdivided into letters A, B, C, etc. (from the upper to the lower axis), setting up a coordinate chart for the assessment of the tumor bed.

Data were entered into Excel and later exported to the Statistical Package for Social Sciences (SPSS), version 20.0, for statistical analysis. Categorical variables were described by frequencies and percentages. Symmetry of quantitative variables was verified using the Kolmogorov-Smirnov test. Quantitative variables were described by mean and standard deviation. Categorical variables were associated using the chi-square test. Quantitative variables were compared between the group with and without PCR using the Student's *t* test for independent samples. OS and disease-free survival (DFS) were assessed using the Kaplan-Meier curve and compared between groups using the log rank test. Factors associated with PCR with a p-value of less than 0.05 in the bivariate analysis or those considered to be potential confounders were included in a multivariate Cox regression analysis. A significance level of 5% was considered for the established comparisons.

The OS was analyzed from the date of diagnosis to the date of death or last follow-up (patients who lost follow-up), and the DFS was analyzed from the date of diagnosis to the date of disease progression (locoregional recurrence and/or distant recurrence), date of death (patients who did not show disease progression and evolved to death) or date of last follow-up (patients who lost follow-up).

RESULTS

One hundred and seventy-six patients with BC were submitted to NACT at the UNACON of the GH and in the private practice from March 2012 to June 2020. All were included in this analysis. Table 1 shows the clinical characteristics of the population.

The patient population in this sample had a median age of 47.3 years (ranging 24 – 77). It was observed that approximately half of the patients (n = 94; 53.5%) were aged between 35 and 49 years. Regarding the body mass index (BMI), it was noticed that the majority (n = 116; 65.9%) had a BMI ≥ 25. Furthermore, 86.4% (n = 152) had non-special invasive ductal carcinoma as histological subtype and 40.3% (n = 71) of the patients presented histological grade 3. The most frequent molecular subtypes were luminal B/HER2 negative (n = 60; 34.1%) and triple negative (n = 46; 26, 1%), and most patients were in clinical stage (CS) IIB (n = 56; 31.8%) and IIIA (n = 52; 29.5%). Of these patients, 145 (82.4%) received regimens based on anthracyclines and taxanes in NACT, 13 (7.38%) received anthracyclines, taxanes, and carboplatin in NACT, and 18 (10.22%) received other regimens. Fifty-eight (32.9%) patients received trastuzumab concomitantly with taxane in neoadjuvant therapy and only nine (5.11%) received pertuzumab concomitantly with taxane and trastuzumab. Only four HER2 positive patients did not receive trastuzumab in neoadjuvant therapy due to delayed delivery of the medication by the Unified Health System (*Sistema Único de Saúde* – SUS), but received it during adjuvant treatment.

Regarding the surgical modality, we observed that 84 patients underwent quadrantectomy, 36 adenomastectomy, 10 skin-sparing mastectomy, 39 modified radical mastectomy, and seven did not undergo surgery due to disease progression. According to

international recommendations, 162 (92%) patients underwent adjuvant radiotherapy after surgery.

After evaluating the surgical specimen, we observed that 62 patients (35.2%) had PCR and 114 (64.8%) did not have PCR.

Analyzing all clinical characteristics of patients who entered *versus* those who did not enter PCR, it was possible to observe a significant association between the molecular subtype and the presence of PCR (P = 0.001). By the adjusted analysis of previously standardized subcategories, it is possible to detect that patients with the triple negative and HER2 positive subtype had a statistically significant higher frequency of PCR, and that the luminal B/HER2 negative subtype had a significantly lower percentage of PCR (p = 0.01) (Table 2).

Table 1. Characteristics of the population.

Clinical characteristics	Categories	Number of patients	%
Total		176	100
Age (years)	< 35	15	8.5
	35–49	94	53.5
	50–64	59	33.5
	≥ 65	8	4.5
BMI	< 18.5	3	1.7
	18.5–24.9	57	32.4
	≥ 25	116	65.9
Histological Subtype	Lobular	3	1.7
	Ductal	152	86.4
	Medullary	14	8
Histological Grade	Others	7	3.9
	I	12	6.8
	II	57	32.4
	III	71	40.3
	Not rated	36	20.4
Molecular Subtype	Luminal A	9	5.1
	Luminal B/HER2 negative	60	34.1
	Luminal B/HER2 positive	33	18.8
	HER2 positive/ non luminal	28	15.9
	Triple negative	46	26.1
Clinical Stage	I IIA	4 34	2.3 19.3
	IIB	56	31.8
	IIIA	52	29.5
	IIIB	24	13.6
	IIIC	6	3.4

BMI: body mass index.

Pathological characteristics such as histological grade, ER expression, RP expression, and HER2 status are associated with PCR with statistical significance, with p = 0.022, p = 0.01, p = 0.01, and p = 0.02, respectively. The other clinicopathological characteristics analyzed, such as age, clinical stage, and Ki-67, did not show a significant correlation with PCR, with p = 0.92, p = 0.248, and p = 0.749, respectively, which demonstrates that they did not influence the outcome of PCR of this sample (Table 3).

Multivariate analysis by Cox regression showed that patients who presented PCR had better OS regardless of clinical characteristics related to the molecular subtype, ER, PR, and Ki67 (hazard ratio — HR = 0.15; 95%CI 0.04 – 0.54) (Appendix 2).

The median follow-up was 35.9 months. The five-year DFS for the total sample was 88.8%, for the group with PCR it was 96.7% and, for the group without PCR, it was 83.2%, with a difference in the limit of statistical significance between groups (p = 0.05) (Figure 1).

The estimated five-year overall survival was 77.8%. When patients were categorized into two groups, with and without CPR, it was possible to observe a significant difference in the estimate of overall survival at five years, with 95.5% in the group with PCR and 69.1% in that without PCR (p = 0.017) (Figure 2).

Among the 176 patients in the total sample, 11 evolved with locoregional recurrence (LRR) (6.25%); one LRR in the group with PCR (1.6%) and 10 LRR were in the group without PCR (8.8%) (p = 0.10).

DISCUSSION

Among the 176 patients with BC who underwent NACT in our study, the PCR rate was 35.2%. Currently, one of the main benefits of NACT is the prognostic information obtained by the pathological evaluation of the tumor bed and axillary lymph nodes after surgery. The PCR is strongly associated with a better prognosis of patients undergoing NACT, as observed in the NSABP B-18 and B-27 clinical trials[11,16].

In our study, we observed a significant association between the molecular subtype and the presence of PCR (p = 0.001), with

Table 2. Association between molecular subtype and PCR.

Molecular Subtype	No. of patients	No. of patients who reached PCR (%)	p-value
Luminal A			p=wss
Luminal B/HER2 negative			p=0.01
Luminal B/HER2 positive			p=0.01
HER2 positive non luminal			p=0.01
Triple negative			p=0.01

wss: without statistical significance.

PCR rates ranging from 22 to 50% according to the molecular subtype. This finding is consistent with the literature, in which PCR rates are higher in patients with HER2 positive BC and triple negative BC (TN) when compared to patients with HER2 negative/hormone receptor positive BC[14,17].

In line with data from the world literature, we demonstrated that patients who achieved PCR had significantly higher survival rates compared to those with residual disease. In our study, the five-year DFS for the group with PCR was 96.7% *versus* 83.2% for the group without PCR (p = 0.05). The estimated five-year OS for the group with PCR was 95.5% *versus* 69.1% for the group without PCR (p = 0.017). Furthermore, among the patients in our total sample, 11 evolved with LRR (6.25%); one LRR in the group with PCR (1.6%) and 10 LRR were in the group without PCR (8.8%). In the NSABP B-18 study, patients who had post-NACT PCR had longer DFS and greater OS (HR = 0.47, p = 0.0001 and HR = 0.32, p = 0.0001, respectively)[18].

A therapy based on the assessment of prognostic and predictive factors enables the application of different therapeutic modalities used in cancer treatment with the intensity and effectiveness that are adequate and individualized for each specific patient[19]. In our study, pathological characteristics such as histological grade, ER expression, PR expression, and HER2 status are associated with PCR with statistical significance, with p = 0.022, p = 0.01, p = 0.01, and p = 0.02, respectively. The other clinicopathological characteristics analyzed, such as age, clinical stage, and Ki-67, did not show a significant correlation with PCR, with p = 0.92, p = 0.248, and p = 0.749, respectively, demonstrating that they did not influence the outcome of PCR in this sample.

The population in our study consisted mostly of young patients; 53.5% of them were aged between 35 and 49 years and had tumors in more advanced stages, and 61.3% had clinical stage IIB (31.8%) and IIIA (29.5%). However, clinical stage and age did

Table 3. Clinicopathological characteristics according to complete pathological responde (PCR).

Characteristics		All	PCR	Without PCR	P
			N (%)	N (%)	
Total		176	62	114	
Age (years), mean ± SD		176	46.0 ± 11.7	48.0 ± 10.1	p = 0.25
Age (years)	< 35	15	9 (14.5)	6 (5.3)	p = 0.92
	35–49	94	32 (51.6)	62 (54.4)	
	50–64	59	18 (29.0)	41 (36.0)	
	≥ 65	8	3 (4.9)	5 (4.3)	
Histological grade	I	12	2 (3.2)	10 (8.7)	p = 0.022
	II	57	16 (25.8)	41 (36.0)	
	III	71	31 (50.0)	40 (35.1)	
	not available	36	13 (21.0)	23 (20.2)	
Clinical Stage	I	4	1 (1.6)	3 (2.6)	p = 0.249
	IIA	34	12 (19.4)	22 (19.3)	
	IIB	56	19 (30.6)	37 (32.5)	
	IIIA	52	17 (27.4)	35 (30.7)	
	IIIB	24	10 (16.1)	14 (12.3)	
	IIIC	6	3 (4.9)	3 (2.6)	
ER	0–9	73	36 (58.1)	41 (36.0)	p = 0.01
	10–49	15	6 (9.7)	9 (7.9)	
	≥ 50	84	20 (32.2)	64 (56.1)	
PR	0–9	89	43 (69.4)	51 (44.7)	p = 0.01
	10–49	30	8 (12.9)	22 (19.3)	
	≥ 50	52	11 (17.7)	41 (36.0)	
Ki-67	< 14	11	3 (4.8)	8 (7.0)	p = 0.749
	≥ 14	165	59 (95.2)	106 (93.0)	
HER2	Positivo Negativo	62 114	29 (46.8) 33 (53.2)	33 (28.9) 81 (71.1)	p = 0.02

ER: estrogen receptor; PR: progesterone receptor.

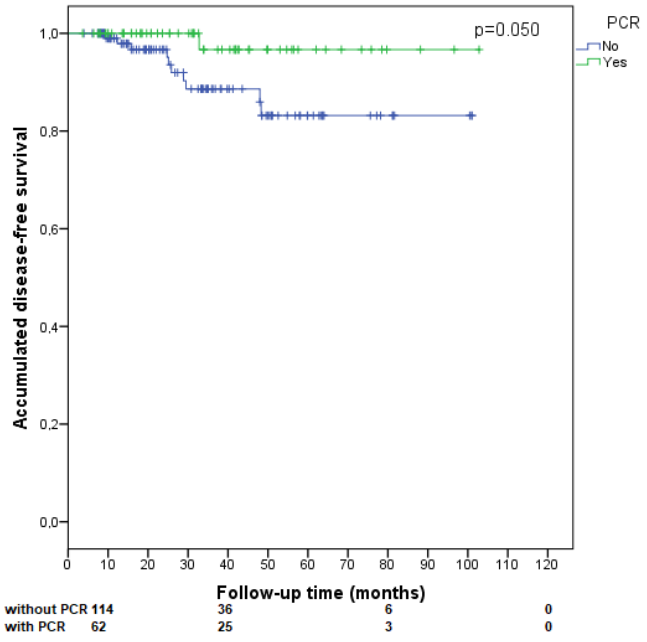

Figure 1. Disease-free survival estimate of patients according to the PCR.

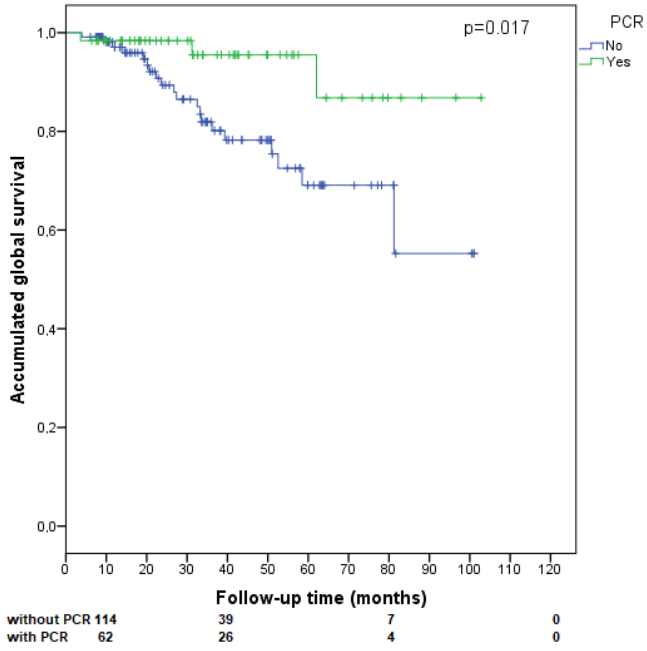

Figure 2. Estimate of overall survival in patients according to PCR.

not have a significant correlation with PCR, which shows that age and tumor size at diagnosis probably do not influence PCR rates in the neoadjuvant setting.

NACT is equivalent in OS compared to adjuvant chemotherapy in the treatment of BC. In contrast to adjuvant treatment, NACT has traditionally been relegated to patients with locally advanced, initially inoperable BC. However, NACT has played an increasingly important role in the treatment of early-stage disease[10], especially in patients with triple negative BC and HER2 positive, regardless of patient age, with benefits even in elderly patients in good clinical condition.

Another key point in the neoadjuvant scenario is the proper interaction between the pathologist and the surgeon, as the former needs adequate clinical and imaging information, such as tumor size and location, in addition to the presence or absence of a clip in the tumor bed for a careful evaluation of the residual tumor. This was a positive point of our work: the pathologist presented this necessary and important information before the macroscopic examination of the surgical specimen, directing it to specific serial sections post-NACT according to well-established international recommendations and allowing the anatomopathological result to mirror the extension of post-NACT residual tumor with high accuracy[15].

Although our study has shown relevant and expected data according to the world literature, we understand that the limitations of this work are related to the small sample, the retrospective nature, and the short follow-up time. In addition, we also observed that a small sample of patients (5.11%) underwent double HER2 blockade in neoadjuvant therapy.

CONCLUSION

In our sample of patients with BC undergoing NACT, we observed higher rates of PCR in the triple negative and HER2 positive molecular subtypes. PFS and OS rates were significantly better in patients who achieved PCR, regardless of clinicopathological factors. We also observed lower LRR rates in the population that reached PCR. Thus, we increasingly emphasize the importance of NACT in the approach of the initial BC.

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AUTHORS' CONTRIBUTIONS

R.F.: Conceptualization, Data curation, Formal analysis, Writing — original draft.
Maximiliano Cassilha Kneubil: Conceptualization, Data curation, Formal analysis, Writing — original draft.
J.B.: Project administration, Methodology, Writing — review & editing.
L.H.B.L.T.: Investigation, Writing — review & editing.
K.B.G.: Methodology, Data curation, Formal analysis.
I.E.L.: Methodology, Project administration, Validation.
M.R.E.: Project administration, Writing — review & editing.
J.A.P.H.: Project administration, Writing — review & editing.

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Apêndice 1. Ficha de avaliação.

Nome: _____ Prontuário:_____

Data de nascimento: ___/___/___ Idade ao diagnóstico: _____

Sexo: ☐ 1. Feminino; 2. Masculino

Etnia: ☐ 1. Branca; 2. Negra; 3. Asiática 4. Parda; 5. Outra.

IMC: _____ Peso: ____ kg Estatura: ____ cm

Performance status: ☐ 0. 0; 1. 1; 2. 2; 3. 3; 4. 4

História prévia de tabagismo: ☐ 0. Não 1. < 20 maços/ano 2. > 20maços/ano

Status menopausal: ☐ 0. Pré-menopausa; 1. Pós-menopausa

Data do diagnóstico: ___/___/___ Laboratório:_____

Tipo histológico: ☐ 1. Lobular invasor; 2. Ductal invasor; 3. Outros _____

Grau histológico (Nottingham): ☐ 1. G1; 2. G2; 3. G3 99. Não disponível

Expressão ER: ☐ valor:_____ 0. Ausente (0%); 1. Baixa (≥ 1% e < 10%); 2. Positiva (≥ 10% e < 50%); 3. Fortemente positiva (≥ 50%)

Expressão PgR: ☐ valor:_____ 0. Ausente (0%); 1. Baixa (≥ 1% e < 10%); 2. Positiva (≥ 10% e < 50%); 3. Fortemente positiva (≥ 50%)

HER2: ☐ 0. 0+; 1. 1+; 2. 2+; 3. 3+; 99. Não disponível

Se 2+: ☐ 0. FISH não amplificado; 1. FISH amplificado; 88. Não se aplica 99. Não disponível

Ki67: ☐ valor:_____ 1. Baixo (< 14%); 2. Alto; 3. Não disponível

Subtipo Molecular: 1.Luminal A 2.Luminal B 3.Luminal-HER2 Positivo

4. HER2 Puro 5. Triplo Negativo

TNM inicial

T: ☐ valor:_____(cm) 0. T1mi; 1. T1a; 2. T1b; 3. T1c 4. T2; 5. T3; 6. T4a; 7. T4b; 8. T4c; 9. T4d

T: ☐ Avaliado por: 0. Exame Físico; 1. Ecografia mamária bilateral; 2 Ambos

N: ☐ 0. N0; 1. N1; 2. N2a; 3. N2b; 4. N3a; 5. N3b; 6. N3c

M: ☐ 0. M0; 1. M1

Estádio clínico: ☐ 1. IA; 2. IB; 3. IIA; 4. IIB; 5. IIIA; 6. IIIB; 7. IIIC; 8. IV

Se 8 (EC IV), sítio metastático: ☐ 8a. Fígado; 8b. Pulmão, pleura ou derrame pleural; 8c. Osso; 8d. SNC ;

8e. Outros _____

TRATAMENTO SISTÊMICO NEOADJUVANTE

Quimioterapia neoadjuvante: ☐ 0. Não realizou; 1. Realizou

Se 1, protocolo ☐ (ver Anexo 1)

Data início:___/___/___ Data término:___/___/___ Nº ciclos:_____

Progressão em vigência de quimioterapia neoadjunte: 0. Não 1. Sim

Terapia de alvo molecular ☐ 0. Não realizou; 1. Trastuzumab; 2. Lapatinib; 3. Pertuzumab 4. Trastuzumab+Pertuzumab 5. Trastuzumab+Lapatinib 6. Outra

Data início:___/___/___ Data término:___/___/___ Nº ciclos:_____

Resposta patológica completa: ☐ 0. Não 1. Sim 88. Não se aplica

Tumor residual ypT___ valor:____(cm) ypN____(___/___)

TNM Patológico pós-quimioterapia neoadjuvante

yT: valor:_____(cm) 0. T1mi; 1. T1a; 2. T1b; 3. T1c; 4. T2; 5. T3; 6. T4a; 7. T4b; 8. T4c; 9. T4d; 10. Carcinoma ductal ***in situ*** 88. Não se aplica

yN: ☐ 0.N0; 1.N1; 2.N2; 3.N3 88. Não se aplica

Laboratório AP Cirurgia:_____ ICR:_____

Se não houve resposta patológica completa, Tumor residual: ☐ 0. CDIS; 1. Carcinoma Invasor; 2. CDIS+Carcinoma invasor

Tipo histológico: ☐ 1. Lobular invasor; 2. Ductal invasor; 3. Outros _____88. Não se aplica 99. Não disponível

Grau histológico (Nottingham): ☐ 1. G1; 2. G2; 3. G3 88. Não se aplica 99. Não disponível

Se não houve resposta patológica completa. ☐ 1. Doença estável; 2. Resposta parcial; 3. Progressão da doença

Em caso de progressão de doença. ☐ 0. Local; 1. Regional; 2. Locorregional

IMH do tumor residual 0. Não realizada; 1. Realizada

Se realizada:

Expressão ER: ☐ valor:_____ 0. Ausente (0%); 1. Baixa (≥ 1% e < 10%); 2. Positiva (≥ 10% e < 50%); 3. Fortemente positiva (≥ 50%)

Expressão PgR: ☐ valor:_____0. Ausente (0%); 1. Baixa (≥ 1% e < 10%); 2. Positiva (≥ 10% e < 50%);3. Fortemente positiva (≥5 0%)

HER2: ☐ 0. 0+; 1. 1+; 2. 2+; 3. 3+; 4. Não disponível

Se 2+: ☐ 0. FISH não amplificado; 1. FISH amplificado; 2. Não disponível

Ki67: ☐ valor:_____1. Baixo (<14%); 2. Alto; 3. Não disponível

CIRURGIA
Cirurgia: ☐ 0. Não; 1. Sim Data: ___/___/___ 88. Não se aplica 99. Não disponível
Se sim: ☐ 1a. Setorectomia/Quadrantectomia; 1b. Adenomastectomia (*nipple sparring*); 1c. Mastectomia (*skin sparring*); 1d. Mastectomia radical modificada
Linfonodo sentinela: ☐ 0. Não realizado; 1. Realizado
Se 1: ☐ 1a. Negativo; 1b. Positivo (___/___)
Se 1b: ☐ 1ba. Micrometástase (<2mm); 1bb. Macrometástase
Esvaziamento linfonodal: ☐ 0. Não; 1. Sim (___/___) Se 1, presença de extravasamento extracapsular: ☐ 1a. Não; 1b. Sim

RADIOTERAPIA ADJUVANTE
Radioterapia adjuvante: ☐ 0. Não; 1. Sim _____Gy _____sessões
Se sim: ☐ 1a. ELIOT; 1b. Mama; 1c. Mama + *boost* leito tumoral; 1d. Mama + áreas de drenagem; 1e. Plastrão 1f. Plastrão+áreas de drenagem
1g. outro _____

TRATAMENTO SISTÊMICO ADJUVANTE
Quimioterapia adjuvante: ☐ 0. Não realizou; 1. Realizou
Se 1, protocolo ☐ (ver Anexo 1)
Data início:___/___/___ Data término:___/___/___ Nº ciclos:_____
Terapia de alvo molecular adjuvante ☐ 0. Não realizou; 1. Trastuzumab; 2. Lapatinib; 3. Trastuzumab+Lapatinib 4. Outra
Data início:___/___/___ Data término:___/___/___ Nº ciclos:_____
Hormonioterapia adjuvante ☐ 0. Não realizou; 1.Tamoxifeno; 2. Anastrozol; 3. Letrozol 4. Tamoxifeno+IA 5. IA+Tamoxifeno 6. Exemestane
7. Outro
Data início:___/___/___ Data término:___/___/___ Nº meses:_____
Supressão ovariana: ☐ 0. Não; 1. Sim Nº meses:_____

Progressão de doença: ☐ 0. Não; 1. Sim Data da progressão: ___/___/___
Sítio de progressão: _____
Recidiva locorregional: ☐ 0. Não; 1. Plastrão; 2. Mama ipsilateral; 3. Axila ipsilateral; 4.Fossa supraclavicular; 5. Mama+axila ipsilateral 6. Outro
Data da recidiva: ___/___/___
Carcinoma mama contralateral: ☐ 0. Não; 1. Sim Data: ___/___/__
Paciente vivo: ☐ 0. Não; 1. Sim Se não, data do óbito: ___/___/__
Data do último *follow-up*: ___/___/___
Pesquisador responsável: _____
Data: ___/___/___

ANEXO 1
1. AC (Doxorrubicina+Ciclofosfamida);
2. DC (Docetaxel+Ciclofosfamida);
3. AT (Doxorrubicina+Docetaxel);
4. TAC (Docetaxel+Doxorrubicina+Ciclofosfamida);
5. AC-D* (Doxorrubicina+Ciclofosfamida+Docetaxel)
6. AC-T** (Doxorrubicina+Ciclofosfamida+Paclitaxel);
7. AC-T*** (Doxorrubicina+Ciclofosfamida+Paclitaxel dose densa);
8. T-AC (Paclitaxel+Doxorrubicina+Ciclofosfamida);
9. CMF (Ciclofosfamida+Metotrexato+5-FU);
10. FAC (Ciclofosfamida+Doxorrubicina+5-FU);
11. FAC-D(Ciclofosfamida+Doxorrubicina+5-FU+Docetaxel);
12. FEC100-T (Epirrubicina+5-FU+Ciclofosfamida+Docetaxel);
13. FEC90-T (Epirrubicina+5-FU+Ciclofosfamida+Paclitaxel)
14. Outro _____

Appendix 2. Cox regression tables of factors associated with overall survival.

Model 1

	P	HR	95.0%CI	
			Lower	Upper
PCR	0.003	0.153	0.045	0.524
Age at diagnosis	0.448	0.982	0.938	1.029
PRvalue	0.119	0.982	0.960	1.005
ERvalue	0.678	1.004	0.986	1.022
Ki67value	0.019	1.028	1.005	1.052

HR: *hazard ratio*; CI: confidence interval; PCR: pathologic complete response; PR: progesterone receptor; ER: estrogen receptor.

Model 2

	P	HR	95.0%CI	
			Lower	Upper
RPC	0.003	0.151	0.043	0.528
Molecular subtype	0.044			
Molecular subtype (1)	0.796	0.755	0.090	6.363
Molecular subtype (2)	0.693	1.583	0.162	15.496
Molecular subtype (3)	0.652	1.687	0.174	16.334
Molecular subtype (4)	0.196	3.913	0.494	30.989
Age at diagnosis	0.230	0.973	0.932	1.017

HR: *hazard ratio*; CI: confidence interval; PCR: pathologic complete response.

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ORIGINAL ARTICLE
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Epidemiological profile of women with breast cancer in a public hospital in the Federal District of Brazil

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ABSTRACT

Introduction: In Brazil, for the 2020–2022 triennium, the estimated incidence of breast cancer in women was 66,280/year. It is the most incident type of cancer in all Brazilian regions. Several risk factors are associated with the probable etiology of breast cancer, though the complexity of the disease makes it difficult to define its main cause. **Objective:** To investigate the prevalence of factors associated with breast cancer in an outpatient population at a public hospital in the Federal District, and to verify the epidemiological profile of this population to compare the data obtained with data published in the literature. **Method:** This is a descriptive cross-sectional study, with 115 participants diagnosed with breast cancer undergoing treatment in a highly complex unit of oncology care in the Federal District between July and October 2020. Data collection was done through a questionnaire. The electronic medical record was consulted to complement the data. **Results:** The majority of women were brown, married, with an average age of 52. Hormone therapy was reported by 73.9%, early menarche by only 33.9% and late menopause by 25.2%. Most had children before the age of 30 and more than 80% breastfed. A family history of breast cancer was present in 30.4% of the sample. The consumption of alcoholic beverages was reported by more than half of the women, but the use of cigarettes was denied by the majority. The practice of some physical activity before the diagnosis of cancer was reported by 69.6%. Most were overweight or had some degree of obesity. Non-special invasive carcinoma was the most common type. **Conclusions:** This study showed that the main factors present in the sample were: advanced age, alcohol consumption, use of hormone therapy and overweight.

KEYWORDS: breast neoplasms; risk factors; health profile; women's health.

INTRODUCTION

Breast cancer represents the most common malignant neoplasm in women worldwide and is also one of the most important causes of death in this gender[1]. In Brazil, the estimate of new cases of the disease in females for the triennium 2020-2022 is 66,280 per year, which places it as the most common type of cancer in all regions[2].

For the Federal District, the estimate for the year 2020 is 730 new cases of this neoplasm in women, the second most common, second only to prostate cancer[2].

Although this disease occurs in all parts of the world, the incidence, mortality, and survival rates vary considerably between different regions of the world. The justification for these variations may lie in the different specificities of each population, such as population structure, lifestyle, genetic factors, environment, and health care[1].

Several risk factors are associated with the probable etiology of breast cancer, though, due to the complexity of the disease, it is not yet possible to specifically define the main cause. However, the genetic inheritance of the BRCA-1 and BRCA-2 genes, which are associated with high risk for the development of familial breast cancer, is a good predictor of the genetic cause of cancer[3].

The best known factors that can increase the possibility of breast malignancy include: gender, advanced age, early menarche and late-onset menopause, nulliparity, late primiparity, non-breastfeeding, sedentary lifestyle, obesity, exposure to estrogen (contraceptives and hormone replacement therapy for menopause), family history, genetic mutation, smoking, and alcohol consumption[4,5].

The clinical stage presented by patients at the time of diagnosis is a determining factor in the design of the therapeutic management. Unfortunately, in developing countries, especially those where the majority of the population has low or middle income, most cases of breast cancer are diagnosed at advanced stages due to lack of knowledge or resources[6].

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The objectives of this study were to investigate the prevalence of factors associated with breast cancer in women undergoing treatment at the outpatient clinic of clinical oncology of a tertiary hospital in the Federal District, to verify the epidemiological profile of this population and to compare the data obtained in this study with those in the literature.

METHOD

A descriptive cross-sectional study was carried out with 115 patients diagnosed with breast cancer who were undergoing treatment in a high-complexity oncology unit between July and October 2020.

Sample size was calculated using a tool available in the OpenEpi version 3.0 software. The 200 patients who underwent intravenous (IV) chemotherapy in 2019 at an outpatient level were considered, with a 95% confidence interval. Taking these values into account, the sample would need at least 110 patients in order to be representative.

For data collection, a questionnaire was applied in the form of an interview/anamnesis about socioeconomic aspects, risk, and protection factors that patients could or not have been exposed to during their lives. In order to have access to the histological type of breast cancer of the patient at the time of diagnosis and other information necessary for the study, the electronic medical record was consulted. Patients informed their consent to participate in the research by signing the Informed Consent.

The socioeconomic and epidemiological variables taken into account are: age, education, children, breastfeeding, weight and height (used to calculate the body mass index – BMI), family history, age at menarche, age at first pregnancy, use hormone therapy, physical activity, smoking, and alcohol consumption.

Inclusion criteria were: diagnosis of breast cancer, female patients, 18 years of age or more, having agreed to participate in the research, and signed informed consent. Patients disoriented in time and space, unaccompanied, who could not answer the questionnaire clearly, and patients with a history of a primary tumor other than breast cancer were excluded. In all, two patients were excluded by the first criterion.

Data were stored in Microsoft Office Excel® 2010 spreadsheets, in which a database was built for descriptive analysis through the distribution of absolute and relative frequencies, in order to generate the results in the form of graphics and tables.

This study was approved by the Research Ethics Committee of Centro Universitário do Distrito Federal (UDF) via Plataforma Brasil (approval number: 4.115.051/2020).

RESULTS

Of the total of 115 patients who participated in the survey, the mean age was 52.8 years (ranging from 28 to 80), most declared themselves brown (55.7%), 52.1% had completed high school or high education degree, 38% were married, with a family nucleus composed of one to three people (67%), family income around one to three minimum wages (41.7%), and own housing conditions (61.7%) (Table 1).

Most had their menarche in the age group considered as normal or late, and the use of contraceptives and/or hormone replacement therapies was reported by 73.9% of them. Mean age at first pregnancy was 23.5 years. Most women had menopause in the normal age group (Table 2).

More than 80% breastfed. Of them, 63.5% reported that they did it for a period equal to or longer than one year. Family history of breast cancer in up to fourth degree relatives was reported by 30.4% of the women in the study (Table 2).

Regarding alcoholism, smoking, and physical activity, the former was prevalent in 61.7%. Smoking was prevalent in less than half of the participants (44.3%). The majority (69.6%) reported that they practiced some type of physical activity before the diagnosis of breast cancer.

To interpret the participants' BMI values, the World Health Organization (WHO) classification of nutritional status was used[7].

Most patients were overweight or had some degree of obesity at the time of the interview (Figure 1). In addition to some incomplete medical records, some patients were unable to inform their weight and height. Thus, 10.4% of patients did not have their BMI calculated.

The most prevalent histological type of tumors among the study participants was non-special invasive carcinoma. This type corresponded to 96.5% of the total diagnoses. The other types of cancer identified in the sample were invasive carcinomas, special types (3.5%).

DISCUSSION

The worldwide incidence of breast cancer in black women traditionally used to be lower than in white ones, though the disease was more aggressive. From 2012 to the present day, this reality has been changing and new cases of breast cancer have an almost similar distribution between white and black women[8].

More than 50% of the women were 50 years old or older, with a mean age of 52.8 years. According to *Instituto Nacional de Câncer José Alencar Gomes da Silva* (INCA), the risk of cancer is increased in women after the age of 50 due to cumulative exposure to risk factors and biological alterations[9]. A study carried out in Bahia also showed a greater predominance of people aged 50 years old or older[10].

Of the 115 participants in the present study, 73.9% reported having used hormonal therapy with contraceptives and/or hormone replacement for menopause at some point in their lives, which emerged as an important common risk factor in the population studied. A similar study in South Africa did not associate the use of hormone therapy with breast cancer[6]. The same was observed in Özsoy et al.[11].

Table 1. Socioeconomic data of women assisted in a high-complex oncology care unit. Brasilia, 2020.

Characteristic	N	%
Age range (years)		
< 30	1	0.9
30–39	10	8.7
40–49	30	26
50–59	46	40
60–69	25	21.8
> 70	3	2.6
Mean age	52.8 years	
Ethnicity		
Yellow	11	9.6
White	25	21.7
Black	13	11.3
Brown	64	55.7
Did not declare	2	1.7
Education		
Illiterate	4	3.5
Incomplete Elementary School	34	29.6
Complete Elementary School	10	8.7
Incomplete High School	7	6.1
Complete High School	32	27.8
Incomplete High Education	7	6.1
Complete High Education	16	13.9
Postgraduate studies	5	4.3
Marital Status		
Married	44	38
Single	19	17
Divorced	40	35
Widower	12	10
Family Nucleus		
Alone	10	8.7
1–3 people	77	67
4–7 people	28	24.3
Family Income		
Less than 1 salary	27	23.5
From 1 to 3 salaries	48	41.7
From 3 to 6 salaries	26	22.6
More than 6 salaries	10	8.7
Did not know	4	3.5
Housing Conditions		
Rent	41	35.7
Owner	71	61.7
Other	3	2.6

Table 2. Biological and behavioral factors involved in the genesis of breast cancer in women treated at a highly complex oncology care unit. Brasilia, 2020.

Characteristics	N	%
Age of Menarche (years)		
≥ 9 and < 10	2	1.7
10–12	37	32.2
13–15	60	52.2
> 15	13	11.3
Did not remembe	3	2.6
Use of contraceptives and/or hormone replacement		
Yes	85	73.9
No	30	26.1
Age of first pregnancy (years)		
15–17	15	13.1
18–21	33	28.7
22–25	22	19.1
26–29	13	11.3
≥ 30	18	15.6
Nulliparas	13	11.3
Did not know	1	0.9
Breastfeeding		
Yes	96	83.5
> 1 year	61	63.5
< 1 year	35	36.5
No	19	16.5
Age of Menopause (years)		
45–49	57	49.6
50–60	29	25.2
Does not apply	29	25.2
Neoplasm in the Family		
Yes	79	68.7
Type of Cancer		
Breast	35	44.3
Ovary	2	2.5
Others	42	53.2
No	36	31.3
Alcoholism		
Former drinker	66	57.4
Yes	5	4.3
No	44	38.3
Smoking		
Former smoker	46	40
Yes	5	4.3
No	64	55.7
Practice of physical activity prior to diagnosis		
Yes	80	69.6
No	35	30.4

In the "AMAZONA III" study, both in the group of women undergoing treatment in the private network and in the group receiving care from the public network, it was observed that more than half had undergone hormonal therapy during their lifetime[12].

However, some studies claim that the risk of developing breast cancer influenced by contraceptive therapy and hormone replacement therapy can decrease or even zero over the years of its interruption. Sun et al. stated that after two years of discontinuation of contraceptives, the risk of developing cancer significantly decreases and, after 10 years, this correlation is null[5].

Given this scenario, the best thing to be done is to guide patients who use hormone therapy to adopt preventive measures, to make periodic consultations with the mastologist, and to perform tests in the presence of any suspicious changes.

The Brazilian Society of Pediatrics considers, for women: precocious puberty those that start before the age of eight; late puberty as the ones that start after 13 years of age; and normal when it occurs between 8 and 13 years of age[13]. Rojas and Stuckey bring studies that showed early menarche as a risk factor for breast cancer, as this is the moment that starts ovulation cycles, which increase women's exposure to endogenous estrogen[14].

None of the women in this study had menarche at an early age. Oliveira et al. observed most women with menarche in the normal age group[15], corroborating the data found in the study by Santos et al.[16].

Normal menopause occurs between the ages of 40 and 55 years. It is considered early when it occurs before 40 years of age and late after 55 years of age[17].

The later the menopause occurs, the longer women are exposed to breast-stimulating hormones, estrogen and progesterone. A relative risk of two was found for developing breast cancer in women who went through menopause after age 55 compared to women who went through it before age 45[14,18].

In the present study, only 25.2% of women reported menopause in the age group that includes cases considered late. A study from Paraná and another from Minas Gerais also did not observe a relationship between late menopause and the consulted cases[16,18].

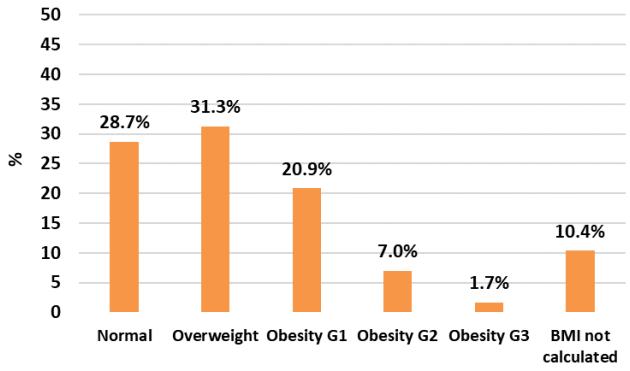

Figure 1. Classification of the participants' body mass index.

Primiparity after the age of 30 is associated with a higher risk of breast cancer, due to the likely cumulative exposure of these women to factors, cited in our study, which have the potential to change breast cells to a neoplastic configuration and which will be stimulated during pregnancy to proliferate. The relationship between nulliparity and the risk of malignant breast cancer is justified by the non-exposure to the benefits of breastfeeding, explained below[19].

The majority of women in our study had their first pregnancy before the age of 30 years. A study from Pará showed a similar result[17].

Breastfeeding is widely known for its protective potential against breast cancer due to the hypoestrogenic state during this period[14]. This protection is provided both in the pre- and postmenopause period[9]. Breastfeeding for at least a year reduces the risk of developing breast cancer by 48%[20].

In this study, 83.5% of the participating women reported having breastfed their children, most of them for a period equal to or longer than one year. Rosa et al.[12], as well as Rocha et al.[18], also reported a high number of women who breastfed.

Regarding the family history of cancer as a risk factor, the literature states that having individuals diagnosed with breast and/or ovarian cancer in the family is related to a higher risk of developing the disease in the breast throughout life due to the hereditary nature of the disease. This risk triples for first-degree relatives[14].

In our data, 30.4% of the women reported having a case of breast cancer in a relative up to the fourth degree in their family. Rocha et al.[18] and Nunes et al.[21] reported a prevalence of breast cancer in the participants' relatives of less than 30%, considering relatives up to the fourth and first degrees, respectively.

Alcohol consumption and its relationship with breast cancer is controversial, but most epidemiological studies demonstrate a consistent relationship between the daily consumption of at least 30 g of alcohol and breast cancer[14]. The consumption of this substance is related to the increase in the levels of hormones associated with estrogen, which trigger the pathway of its receptor[5].

In our sample, alcohol consumption was reported by more than 60% of women, who reported no daily use, only social. Several similar studies did not show a correlation between alcohol consumption and the investigated cases[10,12,18,19]. However, a Brazilian survey showed alcohol consumption in 57% of the sample[22], similar to the data in our study.

Recent studies have associated active and passive smoking with an increased risk of breast cancer and worse survival outcomes[14]. Mutagenic compounds from cigarette smoke have already been found in the breast fluid of non-lactating women, showing the potential for activating oncogenes in the breast through this habit[5].

In our data and in several other studies, it was observed that most women denied exposure to smoking, generating little association of cases in these studies with smoking[10,12,18,19,22].

The regular practice of physical activity is a factor that is related to the protection of women against breast cancer. It is believed that the mechanism that leads to this protection is due to the decrease in body fat, with a consequent reduction in the peripheral conversion of androgens to estrogens by the aromatase enzyme[5,14].

Most of the participants in our study reported doing some kind of physical activity before being diagnosed with cancer. However, 60.9% were overweight or had some degree of obesity at the time of the interview. Rocha et al.[18], revealing data similar to those shown here, reported that more than 70% of the participants were overweight or had some degree of obesity, which shows that obesity is an important factor common to this population.

The most prevalent histological type of breast cancer in the population of this study was non-special type invasive carcinoma (96.5%), but in a smaller quantity there were also special type invasive carcinomas (3.5%). INCA estimates that invasive carcinoma of the non-special type corresponds to the most common type of breast cancer, representing between 70 and 80% of cases. Santos et al.[16], Rocha et al.[18], and Nunes et al.[21] also showed a predominance of the non-special type in their studies.

CONCLUSION

This study showed that the main factors prevalent in the population with breast cancer studied were: advanced age, socially consuming alcohol, use of hormone therapy, and overweight.

The data emphasize the importance of medical follow-up with advancing age. Healthy routines and habits must also continue as breast cancer preventive practices, as well as the promotion of the rational use of hormonal therapies.

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AUTHORS' CONTRIBUTIONS

J.S.J.: Investigation, funding acquisition, investigation, data curation, methodology, project management, formal analysis, writing — review & editing.
F.S.: Administration, supervision, writing — review & editing.
J.V.O.L.: writing — review & editing.

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ORIGINAL ARTICLE
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Trends in bilateral mastectomy for cases of unilateral breast cancer in a Brazilian institute over a 10-year period

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ABSTRACT

Introduction: There has been a substantial increase worldwide in the number of women with unilateral breast cancer who undergo bilateral mastectomy. Possible contributing factors include the advent of nipple-sparing mastectomy (NSM) and an improvement in breast reconstruction techniques. This study evaluated the trend in bilateral mastectomy at the Ceará Cancer Institute in Brazil. **Methods:** Patients with unilateral breast cancer who underwent mastectomy and immediate breast reconstruction were evaluated retrospectively between 2009 and 2018. Clinical, pathological and surgical factors were analyzed to determine their possible effects on the type of surgery performed. **Results:** Of 121 patients, 77 (63.6%) were submitted to unilateral mastectomy, while 44 (36.4%) underwent bilateral mastectomy. Most were treated with NSM (n = 66; 54.5%), with this technique being significantly associated with bilateral mastectomy ($p < 0.001$). Bilateral mastectomy increased significantly over the period ($p = 0.009$; $r^2 = 0.592$), but unilateral mastectomy did not ($p = 0.417$; $r^2 = 0.084$). Age < 45 years ($p = 0.007$) and negative axilla ($p = 0.003$) were also associated with bilateral mastectomy, while axillary dissection was associated with unilateral mastectomy ($p = 0.028$). Multivariate analysis showed the 2016-2018 period to be an independent factor associated with bilateral mastectomy. **Conclusions:** These results corroborate the international literature. From 2010 onwards, there was a trend towards an increase in bilateral mastectomy with breast reconstruction. These data may contribute to multidisciplinary debates, facilitating the establishment of guidelines. Further studies are required to improve understanding of this phenomenon in Brazil.

KEYWORDS: prophylactic mastectomy; unilateral breast neoplasms; mammaplasty.

INTRODUCTION

Breast-conserving surgery is the preferred treatment for early breast cancer. Survival rates after long periods of follow-up are comparable to those achieved with radical mastectomy.[1-6] Currently, the rates of local recurrence are low irrespective of the extent of the surgery;[7] nevertheless, many patients will still undergo mastectomy.

Skin-sparing (SSM) and nipple-sparing mastectomy (NSM) facilitate breast reconstruction and, although no prospective controlled studies have been conducted to evaluate the oncologic safety of these techniques, retrospective studies show adequate local control when compared to radical mastectomy.[8,9]

Recently, various countries have registered increased rates of bilateral mastectomy and a reduction in cases of unilateral mastectomy.[10] Possible explanations include cancer phobia, the possibility of detecting genetic susceptibility to breast cancer,[11] and of immediate breast reconstruction, particularly with the use of implants, following SSN or NSM, with the potential to achieve better breast symmetry,[12] and the greater attention given to the subject by the lay press. This trend, however, has yet to be evaluated in Brazil.

The purpose of the present study was to evaluate this trend in the surgical treatment of breast cancer, specifically bilateral mastectomy and its associated clinical factors, in a setting in which immediate breast reconstruction is available, in women with unilateral breast cancer who were to undergo mastectomy in a reference oncology institute in Brazil.

METHODS

This retrospective, longitudinal study included women with unilateral breast cancer. The internal review board of the Ceará Cancer Institute approved the study protocol under reference

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61.473. Medical records were reviewed and, between 2009 and 2018, patients submitted to mastectomy for the treatment of unilateral invasive breast cancer with recommendation for immediate breast reconstruction were selected. Patients with bilateral breast cancer, breast cancer recurrence or metastatic disease on an initial stage were excluded from the study. The factors evaluated were: whether mastectomy was SSM or NSM, unilateral or bilateral, and the year of the procedure. Data on age, tumor size (T), lymph nodes (N) and molecular subtypes were recorded. Hormone receptor (HR)-positive and HER2-negative tumors were considered luminal, while those expressing HER2 (or FISH/SISH-positive) were classified as HER2, and those that were HR-negative and HER2-negative were considered triple-negative (TN). The type of axillary surgery, adjuvant treatment (chemotherapy, hormone therapy and radiotherapy) and the presence of the inherited pathogenic mutations that predispose to cancer were also evaluated. Clinical outcomes were classified as local and/or regional recurrences, distant recurrences or death resulting from breast cancer. Follow-up of at least three months was required to determine any failure or major complications (skin necrosis, infection or hematoma that required reoperation) in breast reconstruction.

Data were expressed as absolute frequencies and percentages. Associations with the type of mastectomy were determined by using Fisher's exact test or Pearson's χ^2 test. To determine the factors independently associated with unilateral or bilateral mastectomy, the variables with $p < 0.20$ were selected using a forward stepwise approach to build a multinomial logistic regression model.

Linear regression was performed to establish the rate profile of bilateral and unilateral mastectomies over the evaluation period. The SPSS statistical software package for the social sciences, version 20.0 for Windows, was used. A significance level of 95% was adopted throughout the analysis.

RESULTS

The medical records of 341 patients were reviewed and 121 met the inclusion criteria. Between 2009 and 2018, 77 patients (63.6%) underwent unilateral mastectomy, while 44 (36.4%) underwent bilateral mastectomy. Most were treated with NSM (n = 66; 54.5%), a method significantly more common among the patients undergoing bilateral mastectomy ($p < 0.001$) (Table 1).

Bilateral mastectomies were more common in patients < 45 years of age ($p = 0.007$). Of those undergoing bilateral mastectomy, only two had a pathogenic mutation, BRCA, in both cases. T1 (n = 38; 36.2%) and N0 (n = 33, 56.9%) were the most prevalent tumor stage and node status, respectively. Distant metastases were found in 7 patients (8.0%). Node status was significantly associated with bilateral mastectomy ($p = 0.003$) (Table 2).

Table 1. Profile of mastectomies performed between 2009 and 2018.

Total	Mastectomy			
	Total	Unilateral	Bilateral	p-value
	121 (100%)	77 (63.6%)	44 (36.4%)	-
Surgery				
Nipple-sparing mastectomy	66 (54.5%)	31 (40.3%)	35 (79.5%)*	< 0.001
Skin-sparing mastectomy	55 (45.5%)	46 (59.7%)*	9 (20.5%)	
Year				
2009	2 (1.7%)	2 (2.6%)	0 (0.0%)	< 0.001
2010	8 (6.6%)	8 (10.4%)	0 (0.0%)	
2011	4 (3.3%)	3 (3.9%)	1 (2.3%)	
2012	2 (1.7%)	2 (2.6%)	0 (0.0%)	
2013	7 (5.8%)	6 (7.8%)	1 (2.3%)	
2014	23 (19.0%)	22 (28.6%)*	1 (2.3%)	
2015	19 (15.7%)	16 (20.8%)*	3 (6.8%)	
2016	13 (10.7%)	5 (6.5%)	8 (18.2%)*	
2017	10 (8.3%)	3 (3.9%)	7 (15.9%)	
2018	33 (26.3%)	10 (13.0%)	23 (52.3%)*	
Period				
2009-2015	65 (53.7%)	59 (76.6%)*	6 (13.6%)	< 0.001
2016-2018	56 (46.3%)	18 (23.4%)	38 (86.4%)*	

*$p < 0.05$. Fisher's exact test or Pearson's χ^2 test (n; %).

Most tumors were HR-positive (n = 63, 78.8%) and HER-negative (n = 70, 87.5%). Only 9 tumors (11.3%) were TN. Tumor phenotype was similar in the two groups (p > 0.05) (Table 2).

Adjuvant radiotherapy was administered to 53 patients (51.0%) and was not associated with unilateral or bilateral mastectomy (p = 0.116). Ten patients (11.1%) developed postoperative complications and three patients (2.5%) suffered local recurrence, unassociated with the type of mastectomy performed in both cases (p = 0.717 and p = 1.000, respectively) (Table 3). Positive sentinel lymph nodes were found in 62 patients (59.0%), with no difference between the two groups (p = 0.292). Thirty-two patients (30.5%) underwent axillary dissection, which was significantly associated with unilateral mastectomy (p = 0.028). Most of the patients (n = 71; 71.7%) underwent chemotherapy, with no association with the type of mastectomy performed (p = 0.102). Chemotherapy was neoadjuvant in 53% of cases. Most women received hormone therapy (n = 74; 85.1%), which was associated with unilateral mastectomy (p = 0.013). Six deaths occurred (7.5%), unassociated with the type of mastectomy performed (p = 0.092) (Table 3).

Bilateral mastectomy increased significantly (p = 0.009, r^2 = 0.592) over the period. Conversely, unilateral mastectomy did not (p = 0.417, r^2 = 0.084) (Figure 1). The number of bilateral mastectomies was significantly higher than unilateral mastectomies from 2016 onwards (p < 0.001) (Table 1). In the multivariate analysis, the 2016-2018 period was independently associated with bilateral mastectomy, with an odds ratio of 11.53 (95%CI 1.26–105.71) in relation to unilateral mastectomy (p = 0.031) (Table 4).

DISCUSSION

This study found increasing rates of bilateral mastectomy, particularly after 2016. Conversely, unilateral mastectomy did not increase significantly over this period. A study based on the Surveillance,

Table 2. Effect of age at diagnosis, clinical staging and tumor phenotype on the profile of the mastectomies performed.

	Mastectomy			
	Total	Unilateral	Bilateral	p-value
Age (years)				
< 45	39 (44.3%)	15 (31.3%)	24 (60.0%)*	0.007
≥ 45	49 (55.7%)	33 (68.8%)*	16 (40.0%)	
Tumor stage				
T1	38 (36.2%)	20 (32.8%)	18 (40.9%)	0.809
T2	52 (49.5%)	31 (50.8%)	21 (47.7%)	
T3	12 (11.4%)	8 (13.1%)	4 (9.1%)	
T4	3 (2.9%)	2 (3.3%)	1 (2.3%)	
Node status				
N0	33 (56.9%)	14 (40.0%)	19 (82.6%)*	0.003
N1	20 (34.5%)	18 (51.4%)*	2 (8.7%)	
N2	5 (8.6%)	3 (8.6%)	2 (8.7%)	
Metastases				
M0	80 (92.0%)	50 (89.3%)	30 (96.8%)	0.413
M1	7 (8.0%)	6 (10.7%)	1 (3.2%)	
Hormone receptor				
No	17 (21.3%)	6 (13.6%)	11 (30.6%)	0.066
Yes	63 (78.8%)	38 (86.4%)	25 (69.4%)	
HER2				
No	70 (87.5%)	41 (93.2%)	29 (80.6%)	0.104
Yes	10 (12.5%)	3 (6.8%)	7 (19.4%)	
Triple-negative				
No	71 (88.8%)	41 (93.2%)	30 (83.3%)	0.286
Yes	9 (11.3%)	3 (6.8%)	6 (16.7%)	

*p < 0.05. Fisher's exact test or Pearson's χ^2 test (n; %).

Table 3. Additional treatment and outcome according to the type of mastectomy performed.

	Mastectomy			
	Total	Unilateral	Bilateral	p-value
Radiotherapy				
No	51 (49.0%)	28 (43.1%)	23 (59.0%)	0.116
Yes	53 (51.0%)	37 (56.9%)	16 (41.0%)	
Complications				
No	80 (88.9%)	55 (87.3%)	25 (92.6%)	0.717
Yes	10 (11.1%)	8 (12.7%)	2 (7.4%)	
Local recurrence				
No	118 (97.5%)	75 (97.4%)	43 (97.7%)	1.000
Yes	3 (2.5%)	2 (2.6%)	1 (2.3%)	
Positive sentinel lymph node				
No	43 (41.0%)	28 (45.2%)	15 (34.9%)	0.292
Yes	62 (59.0%)	34 (54.8%)	28 (65.1%)	
Axillary dissection				
No	73 (69.5%)	38 (61.3%)	35 (81.4%)*	0.028
Yes	32 (30.5%)	24 (38.7%)*	8 (18.6%)	
Chemotherapy				
No	28 (28.3%)	17 (28.3%)	11 (28.2%)	0.102
Neoadjuvant	32 (32.3%)	15 (25.0%)	17 (43.6%)	
Adjuvant	39 (39.4%)	28 (46.7%)	11 (28.2%)	
Hormone therapy				
No	13 (14.9%)	4 (7.3%)	9 (28.1%)*	0.013
Yes	74 (85.1%)	51 (92.7%)*	23 (71.9%)	
Death				
No	74 (92.5%)	47 (88.7%)	27 (100.0%)	0.092
Yes	6 (7.5%)	6 (11.3%)	0 (0.0%)	

*p < 0.05. Fisher's exact test or Pearson's χ^2 test (n; %).

Epidemiology and End Results (SEER) program showed an increase in contralateral mastectomy in the United States from 1.8% in 1998 to 4.5% in 2003.[13] Simultaneously, conservative treatment remained stable, indicating that the preference for contralateral mastectomy is especially for women undergoing major surgery.[14]

The present rate of bilateral mastectomy was higher compared to earlier studies,[13,14] particularly in cases of NSM. Having selected patients for whom immediate breast reconstruction was available may have affected our results: preservation of the entire skin envelope of the breast facilitates reconstruction involves more discrete scars, and may affect the decision to perform bilateral surgery.[15] A retrospective study by the American National Cancer Database (NCDB) showed that in women submitted to surgery between 1998 and 2011, contralateral surgery increased 7% for each percentage point of increase in reconstruction[16].

More women have opted for bilateral mastectomy despite a paradoxical decline in the rates of contralateral disease in recent years. Following the introduction of systemic treatment, the annual risk of contralateral cancer fell from 0.5% to around 0.1% annually.[17] Overestimation of the risk may have affected the planning of surgeries. Germline mutations such as the BRCA1/2 gene mutations are known to play a role in the appearance of new breast tumors, with bilateral surgery often being recommended in such cases.[18] Nevertheless, in this study, only two patients were confirmed to have one of the inherited gene mutations.[19,20] Most of the prophylactic surgeries were probably performed based on family history and on the patients' personal decisions. A survey showed that only 38.1% of the patients with unilateral breast cancer knew that the contralateral prophylactic surgery had no effect on survival.[21]

Age also affected the results, with 56% of the women under 50 years of age undergoing bilateral surgery compared to 27% of the older patients, and a significant association being found between age < 45 years and bilateral surgeries. Likewise, data from the California Cancer Registry revealed that bilateral surgery was associated with younger age, with the rates increasing from 3,6% in 1998 to 33% in 2011, an increase of almost 10 times within little more than ten years.[22]

Neoadjuvant chemotherapy (NACT), traditionally used in cases of locally advanced cancer, has recently been indicated to facilitate breast conservation also in operable tumors.[23] Paradoxically, its use in the present study was associated with bilateral mastectomy in 53% of cases. A recent NCDB-based study reported similar results following the evaluation of almost 60,000 women submitted to NACT between 2010 and 2014.[24] Despite the increase in full pathological response over the time period, the rates of breast conservation increased slightly from 37.0% to 40.8% (p = 0.22) and bilateral mastectomy rates with immediate breast reconstruction increased from 8% to 13.1%, with a reduction in unilateral mastectomy. In the present study, bilateral surgery increased for patients with aggressive chemosensitive disease (70% of HER2 and 67% of the TN cases), although they would normally be potential candidates for NACT and conservative surgeries. Conversely, in luminal tumors, the bilateral surgery rate was lower: 30% of the cases. Better understanding is required regarding the reason why many patients who are eligible for breast-conserving surgeries decide that mastectomy is necessary. One of the possibilities is the fear of recurrence of the disease and the false impression that mastectomy is a "safer" treatment.[25]

In the present study, bilateral surgery was more closely associated with early-stage breast cancer. Patients with negative axilla were more likely to undergo bilateral surgery, whereas those who had undergone axillary dissection were more likely to have had a unilateral surgery. In general, the impact of a prophylactic surgery tends to be lower in the advanced stages of the disease, which may have affected these results.

Breast reconstruction failure, the most serious local complication in this procedure, was low in the present analysis, irrespective of laterality. In a cohort of 471 patients from Yale University, 58% underwent bilateral surgery, with complication rates being similar to those found with unilateral surgery (re-operation: 11.2% versus 10.8%).[26] Bilateral prophylactic mastectomy was associated with a longer hospitalization period, a factor that was not evaluated in the present study. Most cases of breast reconstruction today are performed with the use of implants, minimizing surgical complications. Women undergoing reconstruction with autologous flaps,[27] which prolongs surgery and increases associated morbidity, were not included in the present study.

Table 4. Multinomial logistic regression for predictive factors of bilateral mastectomy.

	p-value	Adjusted OR (95%CI)
Bilateral mastectomy		
Surgery (NSM) (SSM)	0.431	-
Year (2016-2018)	*0.031*	*11.53 (1.26–105.71)*
Age (< 45 years)	0.322	-
Node (+)	0.375	-
Hormone Receptor (-)	0.218	-
HER2 (+)	0.998	-
Radiotherapy (Yes)	0.874	-
Axillary dissection (No)	0.994	-
Chemotherapy (Yes)	0.938	-
Hormone therapy (No)	0.655	-
Death (No)	1.000	-

*p < 0.05; OR: odds ratio; 95%CI: 95% confidence interval for the adjusted OR; SSM: skin-sparing mastectomy; NSM: nipple-sparing mastectomy.

CONCLUSION

In conclusion, these results corroborate the international literature. From 2010 onwards, there was a trend towards an increase in bilateral mastectomy with breast reconstruction. These data may contribute to multidisciplinary debates, facilitating the

establishment of guidelines. Nevertheless, further studies are required to increase understanding of this phenomenon and the impact it produces in the country.

AUTHORS' CONTRIBUTION

F.P.: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing — original draft, writing — review & editing.

M.V.: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing — original draft, writing — review & editing.

P.G.: Data curation, formal analysis, methodology, resources, software, validation, visualization, writing — review & editing.

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ORIGINAL ARTICLE
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Patient navigation: fighting for the rights of breast cancer patients in Brazil

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ABSTRACT

Introduction: The content of this article deals with the experience of the navigation program for patients in a breast cancer diagnosis center of the State Health Department of Rio de Janeiro. The objective was to show how the patient navigation program can allow the proper application of the 60-day Law, being a topic of interest for the planning and evaluation of actions to control this cancer in Brazil. **Methodology:** The patient navigator accompanied women from the Unified Health System (*Sistema Único de Saúde* — SUS) with a diagnosis of breast cancer to start treatment at a specialized center within 60 days. Information on the clinical characteristics of the patients, clinical dates and barriers encountered were collected. Univariate logistic regression was used to assess factors associated with starting treatment within 60 days. **Results:** From January to July 2020, 301 breast biopsies were performed, 126 (42%) of breast cancer. The mean age was 54 years (26–88). 75% of the lesions were diagnosed in advanced stages (IIB to IV). The mean time to start treatment was 39 days (11–108). The main barriers found were: fear (93%), difficulty in communicating with the medical team (81%), uncoordinated health care (37%). Being treated outside the city of Rio de Janeiro (RJ) was the main factor associated with treatment within 60 days (79.5% ***vs***. 20.5%, $p < 0.001$). **Conclusion:** The integration of the patient browser into work processes contributed to compliance with the 60-day Law in 86% of cases. In the context of a complex and fragmented healthcare system for a population in a situation of socioeconomic vulnerability, the patient navigation program proves to be a tool to increase the rate of law enforcement in Brazil.

KEYWORDS: breast neoplasms; patient navigation; barriers to access of health services; patient rights.

INTRODUCTION

Although there is a trajectory of actions for the prevention and control of breast cancer (BC) in Brazil, the scenario of its high incidence, diagnosis at an advanced stage, and high mortality continues to be constant due to barriers regarding access to health care[1]. The estimate for the 2020-2022 triennium is of about 66,280 new cases per year, with an incidence of 61.61 per 100,000 inhabitants[2]. The crude death rate was 15.4 per 100,000 inhabitants, with 16,069 deaths in 2016. There was an increase of 33.6% in the mortality rate from BC in the period from 1980 to 2016[2].

Approximately 75% of Brazilians are covered exclusively by the Unified Health System (*Sistema Único de Saúde* — SUS), and although progress toward universal health coverage has been made across the country, large disparities that affect cancer care remain[3]. Women treated in SUS have more advanced disease and worse disease-free and overall survival when compared to women treated in private health care facilities (which can be partially attributed to longer delays and advanced stages in diagnosis)[3].

The average time for diagnosis is up to 31 days in the private health care system, with 18% of cases diagnosed in stages III and IV, while in SUS the average is 93 days, and in some cases it can reach up to 180 days, with 40% of cases diagnosed in these advanced stages[4]. In addition, the average age of BC diagnosis in Brazil is 53 years, and 30% to 40% of women are under 50 years of age. This significant portion of women is outside the Ministry of Health's screening recommendation and has more aggressive and faster growing tumors (HER-2 positive and triple negative subtypes)[4,5].

Providing quality cancer care to all patients presents numerous challenges, including difficulties in coordination of and access to care. It is "a community-based service delivery intervention designed to promote access to timely diagnosis and treatment of cancer and other chronic diseases, removing barriers to care"[6]. Patient navigation has been frequently proposed

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and implemented to face the challenges of access to cancer care in high-income countries[7]. There are still few studies on patient navigation interventions in cancer treatment in low- and middle-income countries in Asia, South America, and Africa, but all suggest that the provision of navigation services can improve access to cancer care in these countries[7]. All barriers to accessing healthcare resources affect health, overall survival, and mortality rates, which is why a patient navigation program (PNP) is so important. This can ensure that patients receive the help they need on the cancer journey in low- and middle-income countries, particularly in areas where access to health care is fragmented and health systems may be fragile and underfunded[8].

Recognizing the negative impact of the delay in cancer diagnosis and treatment, in 2012 the Brazilian government issued Law No. 12.732/12 of the Ministry of Health, or the 60-day Law (*Lei dos 60 Dias*). This law establishes that treatment for any type of cancer for patients in the public health system must start within 60 days of the definitive diagnosis[9]. In a recent initiative in Rio de Janeiro (RJ), the effectiveness of patient navigation in the public health system from a diagnostic center was proven through an increase in the rate of compliance with the 60-day Law from 10% to 52%[10]. This study showed the main factors that contribute to compliance with the Law in Rio de Janeiro[11]:

- improvement in the structure and processes of diagnostic services (histopathological report with the identification of the molecular subtype, delivery of the report in a medical consultation, direct insertion into the system regulation, performance of staging exams);
- patient navigator acting on the main barriers (fear and fatalistic thoughts and uncoordinated health care);
- treatment outside the capital of Rio de Janeiro.

The content of this article deals with the experience of navigating patients in a BC diagnosis center of the State Health Department of Rio de Janeiro within a womens's hospital, *Hospital da Mulher Heloneida Studart* (HM), in the city of São João de Meriti (RJ). This diagnostic center serves mainly the Baixada Fluminense (part of the population in Metropolitan Health Region I)[12]. The objective was to offer those interested in the topic, especially managers and health professionals, subsidies to understand, plan and evaluate the actions to control this cancer throughout the continuum of care in which patient navigation intends to allow the proper application of the 60-day Law .

The PNP at HM aims to help women diagnosed with BC start treatment at a specialized center within 60 days. Its target population is women from the SUS with a diagnosis of BC, who need to start treatment at a specialized center. Its main goals are:

- To be successful if at least 70% of women start treatment within 60 days of histopathological confirmation
- To use the results to inform hospitals and health policy makers about the positive results of patient navigation.

METHODS

This is an intervention in a diagnostic service in which a social worker was trained to be a patient navigator (PN) with the responsibility of monitoring patients recruited from the day of the breast biopsy at the HM Imaging Center to the start of treatment at the Reference Center determined by the regulation of the State Health Department of Rio de Janeiro. Inclusion criteria were: women with a diagnosis of BC over 18 years old and attending a public service for consultation regarding a confirmed BC. Exclusion criteria were: no personal documents; patients with private health care insurance; investigation or diagnosis of second primary tumor; patients in the terminal phase of some other disease (prognosis of survival of less than 6 months); uncontrolled comorbidities; history of drug abuse or alcoholism; patients suffering from major psychotic disorders or uncontrolled psychiatric disorders; mentally handicapped patients; incarcerated patients; loss of follow-up.

Contact with the patient took place at least once a week by phone, e-mail, text message or in person. After three consecutive unsuccessful contacts with the patient, navigation was interrupted, this being called loss to follow-up.

Information was collected on the patients' clinical characteristics, clinical dates, barriers encountered, a satisfaction questionnaire, and the Functional Assessment of Cancer Therapy — Breast[13] questionnaire was applied, which includes a list of statements that other patients with BC judged to be important. Descriptive analysis of population characteristics was performed using measures of central tendency and dispersion (continuous variables) and measures of absolute and relative frequency (categorical variables). To assess factors associated with starting treatment within 60 days, a univariate logistic regression was performed.

RESULTS

From January to July 2020, 301 breast biopsies were performed, with 126 (42%) positive cases for malignancy. Twenty-three patients were excluded (6 died before the biopsy result, 7 were not located, and 10 had private health insurance). Table 1 shows the clinical characteristics of the 103 patients enrolled in the PNP of HM and of the 85 patients followed up to the start of treatment after additional exclusions (14 due to loss of follow-up, 3 due to investigation of a second primary tumor, and 1 due to uncontrolled comorbidities).

Mean age was 54 years (26–88 years). Forty percent of patients were under 50 years of age, and 84% reside in *Baixada Fluminense*. Seventy-five percent of the lesions were diagnosed at an advanced stage (clinical stage IIB to IV). As for the biological profile, 59% were classified as luminal, 21% as HER-2 positive, and 20% as triple negative. Women under 50 years of age were more frequently diagnosed at an advanced stage than women over 50 years (81% *vs.* 77%, p = 0.655). HER-2 and triple negative

Table 1. Clinical and treatment characteristics of women with breast cancer (n = 103).

Characteristics	n	%
Age range, in years		
< 50	42	40
≥ 50	61	60
Municipality of residence		
Belford Roxo	12	12
Cabo Frio	05	5
Duque de Caxias	07	7
Japeri	01	1
Mesquita	05	5
Nilópolis	07	7
Nova Iguaçu	25	24
Rio de Janeiro	19	18
São João de Meriti	22	21
Clinical staging at diagnosis		
in situ	00	0
I	03	3
IIA	23	22
IIB	29	28
IIIA	03	3
IIIB	36	35
IIIC	01	1
IV	08	8
Clinical staging at diagnosis		
Initial	26	25
Advanced	77	75
Histological type		
Invasive ductal carcinoma	89	86
Invasive lobular carcinoma	10	10
Ductal carcinoma *in situ*	03	3
Invasive papillary carcinoma	01	1
Grade		
1	06	6
2	78	76
3	19	18
Biological profile		
Luminal A	25	25
Luminal B	35	34
HER-2 positive	22	21
Triple negative	21	20
Family history for breast cancer		
Yes	29	28
No	74	72
Related death		
Yes	01	1
No	102	99
Additional exclusions		
Loss of follow-up	14	14
Second primary tumor	03	3
Uncontrolled comorbidities	01	1
Type of initial treatment*		
Surgery	16	19
Chemotherapy	64	75
Hormone therapy	5	6
Location of referral center for initial treatment*		
Duque de Caxias	28	33
Nova Iguaçu	26	31
Rio de Janeiro	24	28
Cabo Frio	06	7
Espírito Santo	01	1

Initial staging = *in situ* to IIA, advanced = IIB to IV; Family history for breast cancer = at least one first-degree relative diagnosed with: breast cancer before age 50; bilateral breast cancer or ovarian cancer in any age group; women with a family history of male breast cancer; women with a histopathological diagnosis of proliferative breast lesion with atypia or lobular neoplasm *in situ*; women with a personal history of breast cancer; *after additional exclusions n=85.

subtypes were also more frequent in young women (22% and 32% *vs.* 21% and 17%, p=0.197). Twenty-eight percent of patients had a family history of BC. In the 9-month follow-up, 1 death related to BC was observed.

The mean times of the main clinical dates were: 59 days (3–179 days) between the mammography report and the biopsy; 20 days (15–30 days) between the biopsy and the histopathological report; 8 days (0–18 days) between the histopathological report and insertion into the regulatory system (SER/RJ); 32 days (0–90 days) between insertion in the regulation and the first consultation with a breast cancer specialist at the referral center. Eighty-one percent of patients started treatment with systemic therapy, and 66% started treatment in Baixada Fluminense (*Instituto Oncológico de Nova Iguaçu, Hospital Geral de Nova Iguaçu* and *Hospital Jardim Amália de Duque de Caxias*).

The average time to start treatment was 39 days (11–108 days), with an 86% compliance rate. Figure 1 shows the number of cases (%) of BC, according to the time to start treatment.

Table 2 shows the factors associated with treatment within 60 days. Patients who were referred for initial treatment outside the municipality of Rio de Janeiro (Baixada Fluminense, Cabo Frio, and Espírito Santo) were more likely to be treated within 60 days when compared to patients referred for treatment in the municipality of Rio de Janeiro (79.5% x 20.5%, p < 0.001).

The main barriers reported by patients are shown in Figure 2. Fear and fatalistic thoughts were reported by 93% of patients (fear of breast removal, hair loss, chemotherapy side effects, and death and suicidal thoughts). There was a suicide attempt in which the patient reported that, given the possibility of imminent death, she preferred to take her own life as soon as possible. The other barriers identified are attributed to the health system, such as difficulty in communicating with the health team (81%), uncoordinated health care (37%), waiting to start treatment (25%), and the need to redo staging exams (14%).

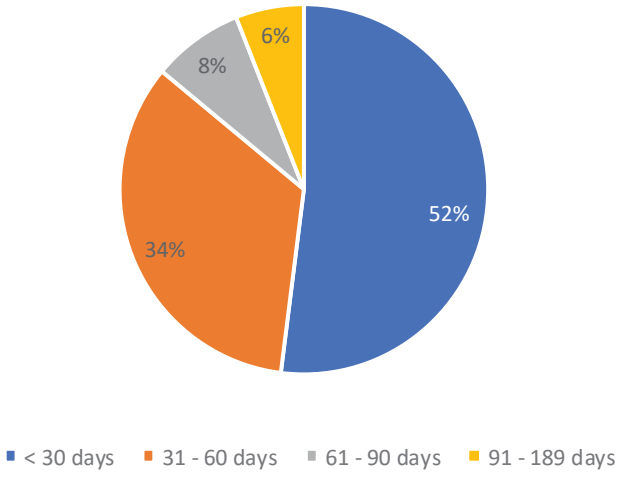

Figure 1. Number of cases (%) of breast cancer according to time to start treatment.

Patients' experience was assessed throughout the entire navigation process. With a score of 1 as a very poor experience and a score of 10 as an excellent experience, patients gave scores of 10, 9, and 8 to their overall experience (95%, 1%, and 4%, respectively). This characterized an excellent performance of the PNP.

Figure 3 shows the patient perception survey with the number (%) of agreement regarding the PN's relationship and services. Gratitude and nurturing and welcoming reception were the prevalent feelings among the patients, as shown by some statements: "I appreciate the reception with a lot of empathy, clearing up doubts, clarifying what was confusing in my head, offering psychological support"; "This awareness and support work is very important in a place that would only be for the delivery of test results"; "Despite the diagnosis, I feel welcomed and confident in the success of my treatment".

Figure 4 shows the responses to the Functional Assessment of Cancer Therapy-Breast questionnaire. This is a multidimensional questionnaire already well validated and used internationally as an instrument to measure quality of life in patients with BC.

Table 2. Factors associated with treatment within 60 days.

Characteristics	Time to start treatment ≤ 60 days (%)	p-value*
Age range (years)		
< 50	42 (57.5)	0.626
≥ 50	31 (42.5)	
Place of residence		
Baixada Fluminense	61 (84)	0.624
Cabo Frio	04 (5)	
Rio de Janeiro	08 (11)	
Clinical staging at diagnosis		
Initial	14 (19)	0.266
Advanced	59 (81)	
Biological profile		
Luminal	42 (57.5)	0.567
HER-2 positive	15 (20.5)	
Triple negative	16 (22)	
Type of initial treatment		
Surgery	11 (19)	0.837
Systemic	59 (81)	
Location of referral center for initial treatment		
Outside the municipality of Rio de Janeiro	58 (79.5)	<0.001
Municipality of Rio de Janeiro	15 (20.5)	

*Pearson's χ^2.

DISCUSSION

To achieve the goals of the PNP at the HM, changes in work processes were necessary, from scheduling the breast biopsy to the start of treatment. The central pillar was to recognize the importance of understanding patients' experiences regarding patient-centered care[14]. The PNP performance was considered excellent by the patients, and the feeling of gratitude and positive experience prevailed.

Cancer is a disease that significantly affects people's lives, both patients and their families. It entails changes in the routine, from the initial commotion in search of an understanding of the diagnosis, after the first symptoms, through the performing of confirmation tests, referral to a specialist, the various visits to care facilities, the costs involved, the interruption of occupational activities, the concern with subsistence, the waiting time for the start of treatment, fears in the face of uncertainty regarding the response to the proposed treatment and, above all, the stigma associated with the diagnosis[15].

The help of the navigator was important to reduce the barriers encountered by patients. The solutions found include: explaining the health system, educating patients about the diagnosis and medical procedures, and showing the importance of attending appointments and taking exams (educational barrier); providing more details about the treatment of the disease and referring patients to support groups or individual psychological support (emotional barrier); explaining about the diagnosis and treatment and advising patients about not being alone in this process and communicating the individual needs of each patient with

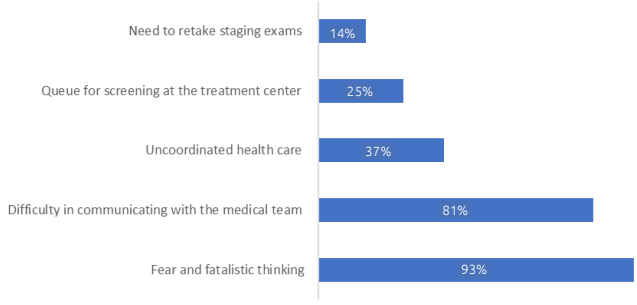

Figure 2. Proportion of barriers reported by patients to start treatment.

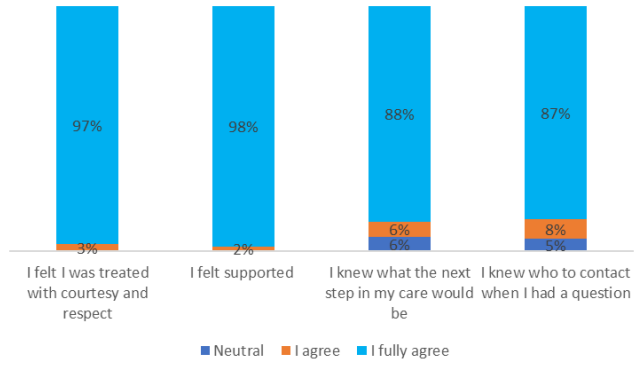

Figure 3. Patient perception survey.

the medical staff (cultural barrier); coordinating appointments for treatment services and ensuring that the tests needed to start treatment are available to doctors (health system barrier)[10].

Historically, cancer is perceived as an intractable and devastating disease, with an outcome directly associated with death. This fact is particularly relevant and can be a source of stress and anxiety for patients[15]. In this study, 52% of patients were stressed with the disease and 72% were concerned that other family members would one day have the same disease. Hence the importance of focusing and listening to patients, seeking to understand the senses and meanings they attribute to experiencing this illness[15].

Seventy-six percent of the patients said they felt little, more or less or not sexually attractive, and 58% managed to feel little, more or less like a woman. It is a process that can be experienced with intense psychological distress in view of the expectations of bodily changes, modification of self-image, impairment of functionality and independence that arise as effects resulting from the indicated treatment, which may involve surgery, chemotherapy, radiotherapy, among other indications. The prevalent issues raised by oncology patients point to the fact that the diagnosis of cancer stimulates emotions and entails a degree of uncertainty and insecurity that include the struggle for dignity and a marked fear for their lifetime[16].

The main barrier reported by patients was fear and fatalistic thoughts (93%), as seen in the pioneer study in *Rio Imagem* in 2018[10] and of Latino populations in the United States[17]. In this sense, the feeling of hope must be encouraged to be part of the patients' trajectory. Despite the fears associated with the disease, it is very important to highlight the current chances of curing and controlling the disease. Maintaining a sense of hope contributes to engaging in possible achievements and positive experiences, despite the changes brought about by the illness. Keeping the routine planning, focusing on achievable activities, preserving the sense of spiritual and/or religious connection, and practicing relaxation activities can contribute to a more hopeful perspective on the scenario that can be disorganizing[18].

In addition, correct, transparent information, transmitted by respectful and careful communication that must be carried out by the health team, facilitates the understanding of the reality of the disease, helping patients in the search for adequate treatment and favoring a more active posture in the process, whilst the lack of information can lead patients to misunderstand their disease, leading them to seek unconventional therapies, often reinforced by the stigma and consequent prejudice against cancer. It is very important that patients find a safe space for care, and the health team involved must be able to offer an active and empathetic approach to emotional issues[18].

Seventy-five percent of the patients had advanced disease at diagnosis, 40% of the patients were considered young, that is, under 50 years of age, and 28% of the patients had a family history of BC, indicating the importance of expanding patient navigation for primary health care[19]. All patients with family risk reported that they were never instructed about the risks of the disease and how to protect their family members (change in lifestyle, screening for high-risk population, genetic counseling, genetic testing, and prophylactic interventions).

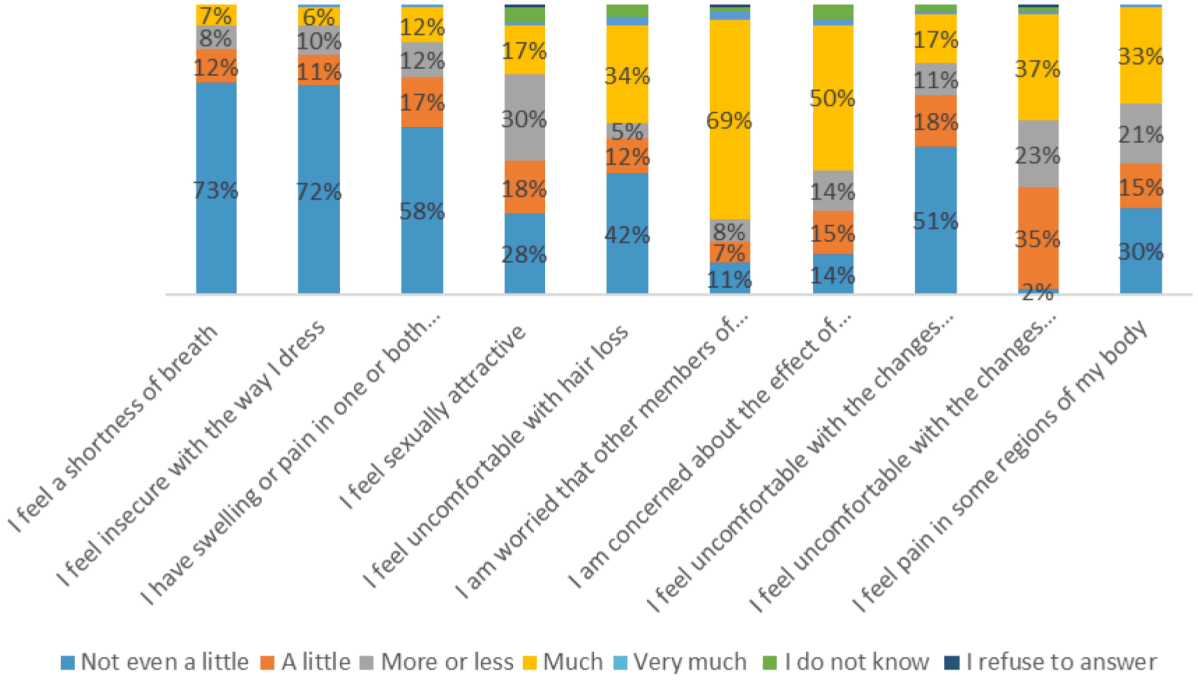

Figure 4. Responses to the Functional Assessment of Cancer Therapy-Breast questionnaire.

Effective actions in the management of care and acting on the main barriers to early detection of BC can favor adherence to personalized mammographic screening, timely investigation, and access to treatment. The PN experience in the Andaraí community, in the municipality of Rio de Janeiro, showed an increase in the tracking rate from 14% to 84%, and 100% of the lesions in 2018 were diagnosed in initial staging[19].

The compliance rate with the 60-day Law was 86%. Medical records and active search of patients diagnosed in HM in 2019 show that the rate of compliance with the law was 27% (Sandra Gioia, HM, personal information, 2020). Thus, the introduction of PN was important to increase compliance with the law, reaching the level considered desirable (above 70%). PN intervention favored the journey of the patients, who, in their majority, needed neoadjuvant chemotherapy and were referred for treatment at the reference centers in Nova Iguaçu (RJ) and Duque de Caxias (RJ) via regulation. And patients with indication for surgical treatment were referred to the General Hospital of Nova Iguaçu. These services do not have waiting lines to start treatment, as seen in services in the city of Rio de Janeiro, which worsened during the COVID-19 pandemic.

Only 20.5% of patients treated in the city of Rio de Janeiro were able to comply with the law, due to the scarcity of places to start treatment. According to a 2017 report by the State Plan for Oncology Care of the State Health Department of Rio de Janeiro, there is a deficit of 14 units in oncology in Rio de Janeiro, 11 of which are in Metropolitan Region I[12]. Most states had a worse rate of compliance with the 60-day Law for cases of BC diagnosed in an out-of-hospital environment, with Rio de Janeiro having the worst performance in all of Brazil (6%)[20]. Compliance with the 60-day law in oncology is an acquired right, and all Brazilians must strive to ensure that it is properly complied with in accordance with current ethics. Given the inability to comply with the law in Rio de Janeiro, the PNP appears as a promising intervention to reverse this situation. And decision-making intends to be within ethical limits and its dilemmas, especially in the approach to the common good, which is based on the connections of all involved, particularly for those who are considered vulnerable[21].

Data observed in the real world with the intervention of navigation show the importance of disseminating good results to the medical community and the population. It is expected that the PNP with BC will become a public health policy in Brazil with exclusive browsers for its area of performance in continuous care[1]. It is also necessary to develop the school and the digital platform for patient navigation to create work organizations based on arrangements of people (health professionals), work processes, and digital technologies to deliver health care with value for the patient, that is, delivering the best outcomes for the patient at a lower cost.

CONCLUSIONS

The introduction of the PNP for BC was considered successful, with an 86% compliance rate for the 60-day Law, but with reservations about the difficulty of complying with the law in the municipality of Rio de Janeiro due to the shortage of human resources and medical supplies.

In the Brazilian context, the PNP can represent an opportunity to properly implement the existing legislation and, as such, it would have a great potential to favor the functioning of the health system in a health care network.

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AUTHORS' CONTRIBUTIONS

S.G.: Formal Analysis, Project administration, Validation, Writing — original draft, Writing — review & editing.

L.B.: Supervision.

M.R.: Data curation.

P.G.: Conceptualization, Methodology, Resources, Funding acquisition, Investigation, Writing — review & editing.

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ORIGINAL ARTICLE
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Impact of the immunohistochemical panel on patients with breast cancer diagnosis cared for in a referral hospital in the state of Amazonas

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ABSTRACT

Objective: To demonstrate the time between the diagnosis of the disease, the result of the immunohistochemical panel and the beginning of specialized treatment in patients diagnosed with breast cancer seen at the Foundation Center of Oncology of the State of Amazonas, from June to November 2018 and in the same period of 2019. **Methods:** The study was part retrospective, based on data from medical records, and part prospective, based on data from patients, and we evaluated the time between diagnosis from the immunohistochemical panel and the beginning of specialized treatment in breast cancer patients. **Results:** 170 patients diagnosed with breast cancer were included, 71 from June to November 2018 and 99 breast cancer patients seen from June to November 2019. The median time between diagnosis and immunohistochemistry results of all patients was 36 days, and comparing the two groups of patients, it was observed that for half of the 2018 patients, the time was less than 105 days, while for half of the 2019 patients, it was less than 27 days. If the times between the result of the immunohistochemical panel and the start of personalized treatment in both groups were compared, it was seen that the median time until the start of treatment was longer for patients in 2018, 94.5 days versus 79 days for patients in 2019. **Conclusion:** There was a decrease in the time between the diagnosis and the result of the molecular panel in 2019 compared to 2018. Achieving this result more quickly provided the choice of personalized treatment for each patient, having an important impact on survival in that population.

KEYWORDS: prognosis; survival; breast cancer; immunohistochemistry; time-to-treatment.

INTRODUCTION

Breast cancer is the most common cancer in women worldwide, accounting for 24.2% of all cases in 2018, with 2.1 million new cases[1]. It is estimated for each year of the 2020/2022 triennium, the diagnosis of 66,280 new cases of breast cancer, with an estimated risk of 61.61 cases per 100,000 women[2].

The increased incidence of cancer is related to the increase in life expectancy, improvement of diagnostic methods and the expansion of screening programs[3]. Most tumors have a slow progression and, if diagnosed early, show a considerable increase in the possibility of cure or improvement in survival[4].

The immunohistochemical study has been used in different situations of breast pathology. Hormone receptors, namely estrogen receptors (ER) and progesterone receptors (PR) and the overexpression or amplification of human epidermal growth factor receptor-2 (HER2), are predictive factors among breast cancer patients[5] and are used to define the treatment and establishment of the disease prognosis associated with clinical and pathological variables, as well as lymph node involvement, tumor size, histological type, tumor grade and surgical margins[6].

The time interval between diagnosis and the start of treatment is important to guide resolving measures[7], since delay can worsen prognosis in breast cancer. There is an association

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between delayed diagnosis and treatment with worse disease-free survival, occurrence of lymph node metastasis, tumor size and late staging, but early detection is related to higher cure rates[8].

Therefore, in Brazil, Law No. 12.732, of November 2012 guarantees cancer patients the right to start treatment within 60 days or less after confirmed diagnosis[9].

Accordingly, the aim of our study was to demonstrate the time between the diagnosis of the disease, result of the immunohistochemical panel and beginning of personalized treatment in patients treated at the Foundation Center of Oncology of the State of Amazonas (FCECON) with a diagnosis of breast cancer, in the period from June to November 2018 and in the same period during 2019.

METHODS

This was an observational, cross-sectional and epidemiological study, composed of a retrospective part based on data from medical records, and a prospective part based on patient data, evaluating the time between the diagnosis according to the immunohistochemical panel and the beginning of specialized treatment in patients diagnosed with breast cancer. General data such as age, clinical stage at diagnosis, histological type, immunohistochemical panel, time between diagnosis and the start of treatment and time between diagnosis and the definitive result of the immunohistochemical panel were evaluated.

The 2017 FCECON management report was used as the basis to define a sample, which says that in one year, 131 patients were diagnosed with breast cancer. Therefore, our sample includes information collected from the medical records of patients diagnosed with breast cancer in the period from June to November 2018. Only records with complete information were entered in the study. In the prospective part, data were collected from patients diagnosed with breast cancer in the period from June to November 2019, with a questionnaire being filled out at the time of the consultation at the start of treatment. A total of 169 patients were evaluated, part retrospective, part prospective, referring to the period from June to November 2018 and 2019.

In 2019, FCECON became part of Roche Laboratory's Roche Testing program, enabling the complete and rapid assessment of the immunohistochemical panel for breast cancer. Previously, the examination was performed in a laboratory outside the city of Manaus, which involved a delay that sometimes exceeded 90 days, so there was an important gain for the institution. Thus, the study aimed to determine whether there was a change in the time between the diagnosis of the disease, the result of the immunohistochemical panel and the start of specialized treatment, comparing the 2018 part and 2019 part, since the institution did not yet have this support in 2018.

The immunohistochemical study was based on the identification of markers: ER, PR, HER2 and ki-67 protein. The classification is performed according to: luminal A (ER- and/or PR-positive, HER2-negative and ki-67 index less than 14%), luminal B (ER- and/or PR-positive, HER2-negative and ki-67 index greater than 14%), overexpressed HER2 (HER2-positive, regardless of the presence of PR and ER), triple-negative (ER-, PR- and HER2-negative) and hybrid luminal (luminal B and HER2 overexpression).

The study was approved by the Research Ethics Committee on June 30, 2019, under No. 3.477.033 and CAAE 16400519.2.0000.0004. In the prospective evaluation, all patients signed an informed consent form.

RESULTS

A total of 170 breast cancer patients were included, 71 from June to November 2018 and 99 from June to November 2019. Most patients were between 40 and 69 years old, accounting for 80% of the women included in the study.

Regarding the histological type of patients, the ductal type was the most frequent among those interviewed in both periods. In assessing the immunohistochemical panel, luminal type A was the most common among patients, while the hybrid luminal type was the least frequent.

Regarding the initial treatment chosen in both periods, surgery was the most frequent; however, there was a significant increase in the percentage of patients who had chemotherapy as initial therapy in 2019, that is, 49.5% of patients in 2019 versus 28.2% in 2018.

The data for all variables listed above are presented in Table 1.

Regarding clinical staging, stage IIA was the most frequent in both periods. The most frequent Breast Imaging Reporting and Data System (BIRADS) classification was class IV, also in the two periods studied (Table 2).

In addition to the clinical characteristics of these patients, the time interval between diagnosis and the immunohistochemical results was analyzed. The median time between diagnosis and immunohistochemistry for all patients was 36 days (median absolute deviation or MAD of 28.9 days). Comparing the two groups of patients, it was observed that for half of the patients in 2018 the time was below 105 days (median), while for half of the patients in 2019 it was below 27 days (Figure 1). According to the non-parametric Mann-Whitney test, it can be concluded that there was a significant difference in time interval from diagnosis to immunohistochemical panel results between the two groups ($P \leq 0.05$).

Regarding the time between the result of the immunohistochemical panel and the beginning of personalized treatment, the median time was 86 days (MAD=74.1). When comparing the times in the two groups, the median time to start of treatment was longer for the 2018 patients – 94.5 days versus 79 days for the 2019 patients. The non-parametric Mann-Whitney test was not statistically significant; however, in the exploratory analysis,

Table 1. Profile of patients according to age, histological type, initial treatment and immunohistochemical panel.

Variable	Total n = 170 (%)	Group	
		Patients from 2018 n = 71 (%)	Patients from 2019 n = 99 (%)
Age (years)			
< 40	19 (11.2)	7 (9.9)	12 (12.1)
40–69	136 (80.0)	59 (83.1)	77 (77.8)
≥ 70	15 (8.8)	5 (7.0)	10 (10.1)
Histological type			
Ductal	149 (87.6)	57 (80.3)	92 (92.9)
In situ	7 (4.1)	7 (9.9)	0
Lobular	7 (4.1)	5 (7.0)	2 (2.0)
Medullary	2 (1.2)	0	2 (2.0)
Other	2 (1.2)	1 (1.4)	1 (1.0)
Papillary	3 (1.8)	1 (1.4)	2 (2.0)
Initial treatment			
Surgery	101 (59.4)	51 (71.8)	50 (50.5)
Chemotherapy	69 (40.6)	20 (28.2)	49 (49.5)
Immunohistochemical panel			
HER2 overexpression	36 (21.2)	8 (11.3)	28 (28.3)
Luminal A	72 (42.4)	36 (50.7)	36 (36.4)
Luminal B	38 (22.4)	15 (21.1)	23 (23.2)
Hybrid luminal	4 (2.4)	4 (5.6)	0
Triple-negative	20 (11.8)	8 (11.3)	12 (12.1)

Table 2. Profile of patients according to clinical staging and Breast Imaging Reporting and Data System classification.

Variable	Total n = 170 (%)	Group	
		Patients from 2018 n = 71 (%)	Patients from 2019 n = 99 (%)
Stage			
IA	8 (4.7)	5 (7.0)	3 (3.0)
IB	14 (8.2)	4 (5.6)	10 (10.1)
IIA	56 (32.9)	26 (36.6)	30 (30.3)
IIB	38 (22.4)	15 (21.1)	23 (23.2)
IIIA	25 (15.3)	10 (15.5)	15 (15.2)
IIIB	25 (14.7)	10 (14.1)	15 (15.2)
IV	3 (1.8)	0	3 (3.0)
BIRADS			
I	1 (0.6)	0	1 (1.0)
II	6 (3.5)	3 (4.2)	3 (3.0)
III	9 (5.3)	6 (8.5)	3 (3.0)
IV	105 (61.8)	46 (64.8)	59 (59.6)
V	49 (28.8)	16 (22.5)	33 (33.3)

BIRADS: Breast Imaging Reporting and Data System.

there was a difference in the interval between the result of the molecular panel and the start of personalized treatment in the 2018 compared to 2019 period (Figure 2).

DISCUSSION

The average age of the women analyzed in the study was close to that reported in other studies with Brazilian patients diagnosed with breast cancer, demonstrating an average age of 51.8 and higher frequency between 41 and 60 years[10]. In the present study, most patients were between 40 and 69, totaling about 80% of the women included.

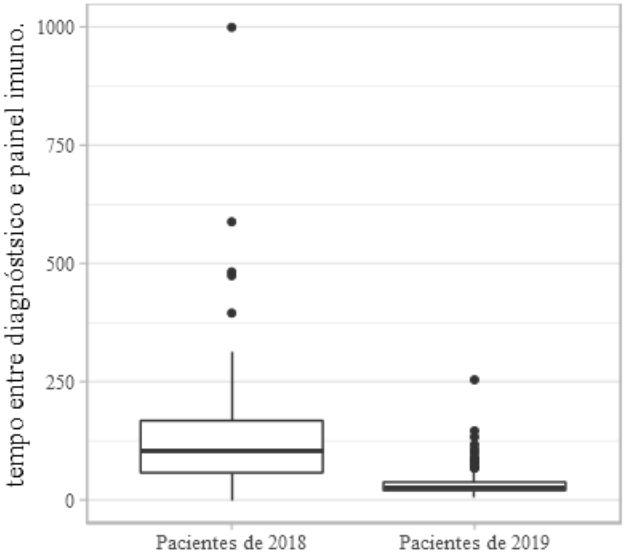

Figure 1. Distribution of time between diagnosis and immunohistochemical results, in days.

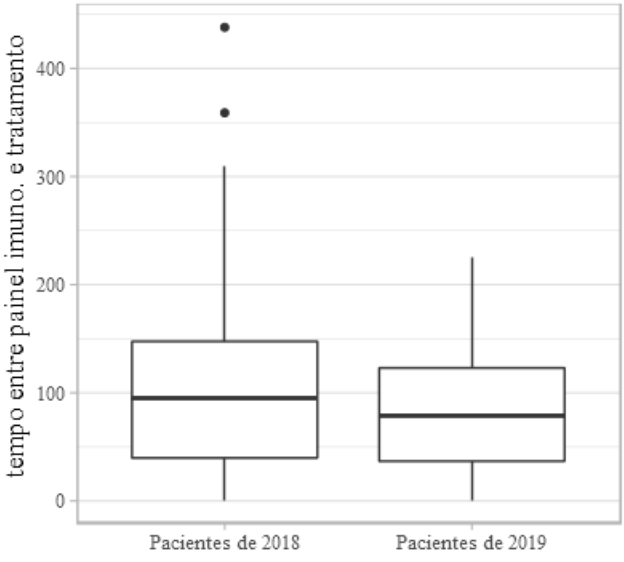

Figure 2. Distribution of time between immunohistochemical results and start of treatment, in days.

Regarding the clinical staging of patients, our data agree with an earlier study that showed a prevalence of clinical stage II in patients[11], as seen in both periods analyzed in our study.

In the BIRADS classification of patients, there was a prevalence of classification IV in both periods, data that agree with what was described in a study in which 34.7% of patients were classified as having BIRADS IV[12].

Regarding the histological type, our finding is similar to that published in another study that demonstrated that 76.9% of the patients analyzed had the invasive ductal histological type[13]. In the present study, 87.6% had this same histological type. Data referring to the immunohistochemical panel of the patients analyzed are in agreement with a study that demonstrated that most of the patients analyzed had luminal A[14].

The prevalent elapsed time interval between diagnosis and immunohistochemical results in the 2018 period agreed with an earlier finding that most of the patients analyzed had a time interval between diagnosis and immunohistochemical examination greater than 90 days[15]. In the 2019 period, most patients obtained their immunohistochemical results within 27 days after diagnosis, a reflection of the integration of FCECON in the Roche Laboratory Roche Testing program, enabling the complete evaluation of the immunohistochemical panel for breast cancer.

In 2019, most patients started treatment within an average interval of 85.8 days after the immunohistochemical results. These data agree with a study that demonstrated that most patients started treatment more than 60 days after immunohistochemical diagnosis[15].

This decrease in the time interval between diagnosis and the result of the immunohistochemical panel in 2019 compared to what was observed in 2018 contributed to the choice of personalized treatment for each patient, which before was often not possible, In 2018, obtaining the immunohistochemical panel was greatly delayed, exceeding the 90-day interval, so treatment was based on the staging of each patient.

In 2018, most patients underwent initial surgical treatment (71.8%), because of this large time interval to obtain the molecular panel results. Thus, many patients who had a triple-negative panel or overexpressed HER2, for example, did not benefit from the appropriate initial treatment for their molecular types. In 2019, with the possibility of obtaining immunohistochemical information sooner, there was a significant increase in patients who received chemotherapy as initial therapy (49.5%), a result of the molecular evaluation that enabled the identification of patients who would benefit from this initial therapy and thereby receive personalized treatment.

CONCLUSION

Immunohistochemical diagnosis is a very important factor in the appropriate choice of initial treatment for breast cancer patients, ensuring personalized treatment for these women. The present study demonstrates the importance of the public-private partnership in improving the times for the diagnosis and treatment of breast cancer.

AUTHORS' CONTRIBUTIONS

H.P.: Writing — original article.
R.P.: Writing — original article.
T.S.: Writing — original article.
H.P.: Writing — original article.
L.A.: Writing — original article.
V.A.: Writing — original article.
M.O.: Writing — original article.
M.S.: Writing — original article.
V.C.: Writing — original article.

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ORIGINAL ARTICLE
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Evaluation of breast cancer in women under 50 in a Mastology service in the Federal District, Brazil

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ABSTRACT

Introduction: Breast cancer is a relevant public health issue, and its incidence has increased in patients aged less than 50 years. This population usually receives a late diagnosis, which contributes with the poor prognosis of the condition. **Objective:** To assess the percentage of patients diagnosed with breast cancer before the age of 50 and compare them with the group that was diagnosed after the age of 50. **Results:** The general mean age was 54 years; 75.68% of the patients were younger than 50 years, aged between 40 and 49 years. Among the ones who were younger than 50, 35.14% were in stage T4; 55.41% underwent neoadjuvant chemotherapy; 16.22% presented distant metastasis; and 10.81%, locoregional metastasis. On the other hand, among those aged more than 50, 22.71% were in stage T4; 30.68% underwent neoadjuvant chemotherapy; 11.36% presented distant metastasis; and 6.82%, locoregional metastasis. **Conclusion:** Breast cancer in women aged less than 50 years in a Mastology service in the Federal District has been a matter of concern, for presenting more advanced tumors at the time of diagnosis; screening is still debatable.

KEYWORDS: breast neoplasms; mammography; mass screening; early cancer detection.

INTRODUCTION

Nowadays, breast cancer is a relevant public health problem. It is the most common malignant neoplasm among women in Brazil and in most of the world, after non-melanoma skin cancer. According to the last global statistics from the Global Cancer Observatory (GLOBOCAN), 2.1 million new cases of breast cancer and 627 thousand deaths caused by the disease have been estimated[1]. Breast cancer screening aims at detecting small asymptomatic tumors, thus contributing with the reduction of mortality. The ultrasound is limited to evaluate microcalcifications; therefore, it is not adequate for the screening of the general population[2,3].

Mammography is the only test whose efficiency is proven for the reduction of breast cancer mortality[4,5]. The Ministry of Health recommends screening mammography for women without signs and symptoms of breast cancer, in the age group between 50 and 69 years, every two years[6,7]. This does not consider an important part of the population (women aged from 40 to 49 years), which responds for about 15%-20% of the breast cancer cases[8]. The Brazilian Society of Mastology (SBM) recommends that breast cancer screening of women with usual population risk be performed through an annual mammography, including women aged from 40 to 75 years, aiming at the early diagnosis and the reduction of mortality[1,8]. After the age of 75, screening mammography is recommended for women whose life expectancy is higher than seven years based on other comorbidities[1,9,10].

Women aged more than 50 years are more prone to developing breast cancer; however, among young women, the clinical, pathological and immunohistochemical characteristics are more aggressive, staging is more advanced, tumor diameter is larger and there are more chances of developing metastasis[11-13]. Since breast cancer is considered as infrequent, younger women should be addressed special attention. A study from 2015 that aimed at understanding the experience of younger women diagnosed with breast cancer, who underwent a mastectomy, pointed out that systemic metastases can occur in 55.3% of the cases in these patients; on the other hand, for systemic metastasis in elderly women, the percentage is 39.2%. The same study also showed that the mortality rate among younger women is 5% higher than among the elderly women[14-16].

Based on the exposed, and considering that breast cancer is the most frequent type of cancer among women around the world, with high mortality rates, being a relevant public health issue, the main objective of this study was to assess the percentage of patients assisted in the Mastology service of Hospital Regional

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de Ceilândia, diagnosed with breast cancer before the age of 50. Finally, it intends to provide subsidies so that public policies can be developed to favor a more efficient and earlier diagnosis, including the coverage and screening of younger women beyond specialized treatment, therefore increasing the chances of cure for these patients.

METHOD

This is a retrospective, cross-sectional, descriptive and observational study carried out to assess the percentage of breast cancer in women, aged less than 50 years, assisted at the Mastology service of Hospital Regional da Ceilândia, from January 2015 to April 2020. The data were collected from the charts of the selected patients, inserted in Excel spreadsheets and statistically evaluated by the Statistical Package for the Social Sciences (SPSS), version 25. Significance level was $p \leq 0.05$. Both the Student's t-test and the χ^2 test were used. This analysis was approved by the Research Ethics Committee, CAAE: 35587420.3.0000.8101.

RESULTS

Our study included 162 patients who met the inclusion criteria, of which 45.70% were younger than 50 years. The general mean age was 54 ± 13.11; the mean of patients younger than 50 years was 42.6 ± 5, and the mean of patients aged 50 years or more was 63.3 ± 9.5.

Of the included patients, 9.80% had family history of breast or ovarian cancer; 84.57% had normal menarche (8-16 years of age); 75.93% were multiparous. For 32.10%, the diagnosed histological type was luminal-B invasive ductal carcinoma (IDC); for 22.22%, it was luminal-A IDC; and for 14.20%, it was triple negative IDC. In 34.57% of the patients, the initial tumor size was T2 (> 2 and ≤ 5 cm); in 28.40%, it was T4; and in 20,99%, it was T3 (> 5 cm). Axillary impairment at physical examination was observed in 38.27% of the patients. For 59.26% of them, a core needle biopsy was performed. Axillary dissection was performed in 50% of them. Neoadjuvant chemotherapy (CT) was performed in 41.98% of the patients, and 37.65% underwent adjuvant CT; 11.11% obtained complete post-neoadjuvant CT response, and 37.65% had partial response. Distant metastasis was observed in 13.58% of the patients, and locoregional metastasis, in 8.64%.

By correlating the patients aged less than 50 years and those aged 50 years or older, we observed that 8.11% of the former had family history of breast/ovarian cancer; 83.7% had normal menarche (8-16 years of age); and 70.27% were multiparous. Of the patients aged 50 years or older, 11.36% had family history of breast/ovarian cancer; 85.23% had normal menarche (8-16 years of age); and 75.93% were multiparous (Table 1).

Patients aged less than 50 years were prevalent in the age group between 40 and 49 years (75.68%). The histological type luminal-B IDC was diagnosed in 33.68% of the patients; luminal-A IDC, in 20.27%; and triple negative IDC, in 16.22%. The initial tumor size was T4 for 35.14% of them; T2, for 27.03% of them; and T3, for 27.03% of them. Of the patients aged more than 50 years, 30.68% were diagnosed with histological type luminal-B IDC; 23.86%, with luminal-A IDC; and 12.50%, with triple negative IDC. The initial tumor size was T2 in 40.91% of them; T4, in 22.73%; and T1, in 20.45% (Table 2).

Table 1. Epidemiological characteristics of women assisted for breast cancer treatment from January, 2015, to April, 2020.

Variables	Group				Total		p-value
	< 50 years		≥ 50 years				
	N	%	N	%	N	%	
Family history of breast/ovarian cancer							
Yes (breast/ovarian)	6	8.11	10	11.36	16	9.88	0.364
No	67	90.54	78	88.64	145	89.51	
Not informed	1	1.35	0	0.00	1	0.62	
Menarcche							
Not informed	11	14.86	10	11.36	21	12.96	0.132
Normal (8–16 years of age)	62	83.78	75	85.23	137	84.57	
Early (< 8 years of age)	1	1.35	0	0.00	1	0.62	
Late (> 16 years of age)	0	0.00	3	3.41	3	1.85	
Parity							
Nulliparous	11	14.86	6	6.82	17	10.49	0.067
Primiparous	10	13.51	6	6.82	16	9.88	
Multiparous	52	70.27	71	80.68	123	75.93	
Not informed	1	1.35	5	5.68	6	3.70	

Of the patients aged less than 50 years, 41.89% presented with axillary impairment at physical examination. Sentinel lymph node biopsy was performed in 60.23% of them, and 44.32% underwent axillary dissection (Table 3).

Of the patients aged less than 50 years, 55.41% underwent neoadjuvant CT, and 35.14% underwent adjuvant CT. There was partial post-neoadjuvant CT response in 47.30% of them, and complete response in 14.86%. Of the patients aged 50 years or older, 30.68% underwent neoadjuvant CT, and 37.65% were submitted to adjuvant CT. There was partial post-neoadjuvant CT response in 37.64% of them, and complete response in 11.11% (Table 4).

Distant metastasis was observed in 16.22%, and locoregional metastasis, in 10.81% of the patients aged less than 50 years. Of those aged 50 years or more, 11.36% presented with distant metastasis, and 6.82%, with locoregional metastasis (Table 5).

DISCUSSION

Family history of breast or ovarian cancer was observed in 3.7% of the patients aged less than 50 years. In relation to those aged more than 50 years, these presented 8.05% more nulliparity and 3.72% more triple negative IDC results; also, 12.41% more initial tumor sizes T4, and 11.12% more initial sizes T3. Younger patients are diagnosed with initial tumor size above T3, which contributes with a poor prognosis. There was axillary impairment (at physical examination) in 6.7% more patients than among those aged more than 50; however, the percentage of 6.76% more axillary dissection procedures was observed among patients aged less than 50. The frequency of neoadjuvant CT was higher than 24.72% among patients aged less than 50 years, who also presented 17.75% more partial post-neoadjuvant CT response and 6.91% more complete response.

In a study carried out by Franzoi et al.[17], the authors identified that 17% of the patients with breast cancer were aged less

Table 2. Clinial and pathological characteristics of patients assisted at Hospital Regional da Ceilândia from January 2015 to April 2020.

Variables	Group				Total		p-value
	< 50 years		≥ 50 years				
	N	%	N	%	N	%	
Age group (years old)							
< 30	1	1.35	0	0.00	1	0.62	0,002
30–39	17	22.97	0	0.00	17	10.49	
40–49	56	75.68	0	0.00	56	34.57	
≥ 50	0	0.00	88	100.00	88	54.32	
Histological type							
HER-2 luminal B IDC	5	6.76	5	5.68	10	6.17	0,656
HER-2 OVEREXPRESSION IDC	4	5.41	10	11.36	14	8.64	
Luminal-A IDC	15	20.27	21	23.86	36	22.22	
Luminal-B IDC	25	33.78	27	30.68	52	32.10	
Luminal HER-2 IDC	4	5.41	4	4.55	8	4.94	
Triple negative IDC	12	16.22	11	12.50	23	14.20	
CDIS HER 2 SUPEREXPRESSO	1	1.35	0	0.00	1	0.62	
Luminal-A ISDC	1	1.35	0	0.00	1	0.62	
Luminal-B ISDC	1	1.35	2	2.27	3	1.85	
Luminal A ILC	1	1.35	2	2.27	3	1.85	
Luminal B ILC	1	1.35	4	4.55	5	3.09	
Triple negative ILC	1	1.35	0	0.00	1	0.62	
Others	3	4.05	2	2.27	5	3.09	
Initial tumor size							
T1 ≤ 2 cm	8	10.81	18	20.45	26	16.05	0,026
T2 > 2 and ≤ 5 cm	20	27.03	36	40.91	56	34.57	
T3 > 5 cm	20	27.03	14	15.91	34	20.99	
T4	26	35.14	20	22.73	46	28.40	

T: size. ISDC: In situ ductal carcinoma; IDC: invasive ductal carcinoma; ILC: infiltrating lobular carcinoma.

than 50 years. In our study, the frequency of patients aged less than 50 years with breast cancer was lower; however, the findings of the authors corroborate ours regarding the fact that younger patients are more symptomatic at diagnosis, often presenting stage III, T3/T4, grade 3, HER-2 positive, luminal-B and triple negative cancer subtypes.

In a study carried out by Laila et al.[18] including 349 women aged between 24 and 90 years, the authors observed that 8.3%

Table 3. Axillary status of women with breast cancer from January 2015 to April 2020.

Variables	Group				Total		p-value
	< 50 years		≥ 50 years				
	N	%	N	%	N	%	
Axillary impairment (at physical examination)							
Yes	31	41.89	31	35.23	62	38.27	0.385
No	43	58.11	57	64.77	100	61.73	
Sentinel lymph node biopsy							
Yes	30	40.54	53	60.23	83	51.23	0.060
No	43	58.11	33	37.50	76	46.91	
Not informed	1	1.35	2	2.27	3	1.85	
Axillary dissection							
Yes	42	56.76	39	44.32	81	50.00	0.274
No	31	41.89	48	54.55	79	48.77	
Not informed	1	1.35	1	1.14	2	1.23	

Table 4. Systemic treatment of women with breast cancer from Janaury 2015 to April 2020.

Variables	Group				Total		p-value
	< 50 years		≥50 years				
	N	%	N	%	N	%	
Neoadjuvant CT							
Yes	41	55.41	27	30.68	68	41.98	0.002
No	33	44.59	61	69.32	94	58.02	
Adjuvant CT							
Yes	26	35.14	35	39.77	61	37.65	0.544
No	48	64.86	53	60.23	101	62.35	
Post-neo CT response							
Complete	11	14.86	7	7.95	18	11.11	0.013
Partial	35	47.30	26	29.55	61	37.65	
Did not undergo it	28	37.84	54	61.36	82	50.62	
Total	0	0.00	1	1.14	1	0.62	

Neo CT: neoadjuvant chemotherapy; CT: chemotherapy.

Table 5. Characterization of the presence of metastasis in women with breast cancer from January 2015 to April 2020.

Variables	Group				Total		p-value
	< 50 years		≥ 50 years				
	N	%	N	%	N	%	
Metastasis							
Yes/distant	12	16.22	10	11.36	22	13.58	0.106
Yes/locoregional	8	10.81	6	6.82	14	8.64	
No	54	72.97	72	81.82	126	77.78	

were aged less than 40 years, and most were diagnosed at early stages; invasive ductal carcinoma was the most common type regarding immunohistochemical characteristics. Most cancers were smaller than 2 cm. In our study, the findings were different: patients aged less than 40 years represented 11.1% of the sample, and less than 50 years, 45.7%. The prevalence of tumor sizes was between 2 and 5 cm, however, in patients aged less than 50 years, they were larger than 5 cm. The prevalent histological type, regardless of age, was luminal-B IDC.

Pereira et al.[19] observed that the age group of 35 to 40 years was the most affected one. In our study, it was 40 to 49 years of age. In an analysis carried out by Magalhães et al.[20], distant metastasis was observed in 3.1% of the sample, and locoregional metastasis, in 0.6%, corroborating the findings of our study, in which distant metastasis was found in 13.58% of the patients, and rates of 4.8% more chances of this type of metastasis in patients aged less than 50, and 4% among patients with locoregional metastasis.

CONCLUSION

Considering the presented study, we can conclude that breast cancer in women aged less than 50 years in a Mastology service of the Federal District has been a reason of concern among these patients, since they present with more advanced tumors at diagnosis, more need for neoadjuvant CT and higher occurrence of metastasis, which reinforces the hypothesis that the reduction in late diagnosis may increase the chances of cure. The highest prevalence among those aged less than 50 years was in the age group of 40 to 49 years, which brings up more discussions about the need for screening.

The review of the official current recommendations of the Ministry of Health for the beginning of breast cancer screening should be a base for public health policies, in order to recruit young women and generate higher rates of diagnosis, better care for the patient and the possibility of an earlier treatment for the disease.

It is important to mention that the lack of access of the population to health also leads to a later diagnosis, and this fact illustrates the urgency for improvements in public health, from the approach of the patient in primary care, providing access to information, until the proper referral to a tertiary service in search for better health indicators.

AUTHORS' CONTRIBUTIONS

A.C.L.V.: Concept, Visualization, Writing – original draft.
L.V.: Project administration, Supervision, Writing – review & editing.
S.P.R.: Data curation, Formal Analysis, Software, Supervision.
S.M.: Investigation, Methodology.

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ORIGINAL ARTICLE
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How, when, and where information about breast cancer in Brazil is found using Google

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ABSTRACT

Introduction: This article sought to clarify the sources that women seek to find information about breast cancer. **Methods:** With a data collection from Google Trends, it was possible to list which keywords are most used when the population performs these searches and to know the volume of searches for the words "breast cancer" (*câncer de mama*), "breast self-exam" (*autoexame de mama*), and "mammography" (*mamografia*) from 2009 to 2019. **Results:** In the search for "breast cancer" (*câncer de mama*), it was seen that the searches for "breast cancer" (*câncer de mama*), "breast cancer symptoms" (*câncer de mama sintomas*), "symptoms of breast cancer" (*sintomas de câncer de mama*), "what is cancer of breast" (*o que é câncer de mama*), and "types of breast cancer" (*tipos de câncer de mama*) are the five most prevalent. Data were also displayed that reflect the importance of the awareness campaign for this type of cancer, the Pink October, since the months of October of the years in question were the ones that had the highest search volume for the keywords "cancer of breast" (*câncer de mama*), "breast self-examination" (*autoexame de mama*), and "mammography" (*mamografia*). In addition, it was noticed that many sites with a greater chance of getting hits due to their being in the first places in the survey did not have the name of the sources from which they had obtained their data and/or the names of the authors, and it was not possible to know the quality of the information published there. **Conclusion:** It is possible to notice the positive effect that the Pink October campaign has, which can contribute to a greater awareness of the importance of breast self-examination and mammography. In addition, it is necessary to be careful when looking for information in the online environment, since not all sites inform the source and/or the name of the author of the article.

KEYWORDS: breast neoplasms; information; mass screening; internet use.

INTRODUCTION

It is known that access to information in the medical field has grown a lot in recent years. Currently, it is possible to know a lot about a certain disease just by going to websites and doing a quick search on what you are trying to answer. Thus, patients have access to vast information about their pathologies and are well informed about their comorbidities. However, where do they look for information?

In his doctoral thesis, Leite Netto conducted a study with 607 women recently diagnosed with breast cancer aged 35 to 74 years old and showed that most of them (83%) used the internet as their main means of communication. When asked where they learned about cancer, 45% said it was on websites and blogs, followed by television and magazines. Although they reported not trusting social media, 66% of the interviewees were users of Facebook, 35% of Instagram, and 15% of Youtube[1].

Google provides a feature called "Google Trends", a free tool that allows you to observe the rise of searches for an established keyword or topic over time.

Therefore, this article aimed to know the prevalence of searches on Google about breast cancer and to know which keywords are most used when the population searches for this type of information. In addition, it sought to find out if the volume of these searches is influenced by the breast cancer awareness campaign, Pink October.

METHODS

This was an analytical cross-sectional study, with data collected in September and October 2020, which aimed to analyze and describe which keywords are most used by the population when doing research on the internet related to breast cancer. The recruited population extended to all those who searched for breast cancer

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and related information on Google, so there is no specific number of people nor a well-defined population characteristic.

In Google Trends, when searching for a keyword, a graphic is provided in which the horizontal axis reflects time and the vertical reflects the volume of searches. Data searched by a few people, searches for the same term that are performed by the same person in a short period of time, and special characters are excluded. The numbers found reflect the trend of search interest for the keyword in a certain region and time frame, where 100 represents the peak of popularity in the search for the word, 50 means that the word has half of the popularity, and similarly, a score of 0 means that the word has less than 1% popularity in searches when compared to the peak. The numbers obtained reflect the percentage of total searches, based on the maximum rating rather than on the total number of hits.

When searching for "breast cancer" (*cancer de mama*) in the field "related searches" and with the filter "main", it was seen that "breast cancer" (*cancer de mama*), "breast cancer symptoms" (*cancer de mama sintomas*), "symptoms of breast cancer" (*sintomas de cancer de mama*), "what is breast cancer" (*o que é cancer de mama*), and "types of breast cancer" (*tipos de cancer de mama*) are the five most prevalent keywords.

An analysis of the search volume of the keywords "breast cancer" (*cancer de mama*), "breast self-exam" (*autoexame de mama*), and "mammography" (*mamografia*) from 2009 to 2019 was also carried out to find out what the variation of this volume over these 10 years and what their relationship with Pink October is. To narrow down the data found, the filters "Brazil" (*Brasil*), "Web search" (*pesquisa na Web*), and the years approached were used.

In addition, a search was carried out in the Google search field with these words to identify which sites feature on the first page and to know whether the articles published there have the description of the author, theoretical framework and/or technical responsible, as well as the body responsible for the website. The facts that being published on the first page of Google searches guarantees 34% more clicks to a website compared to the second page, which receives 19% of clicks[2], and that, according to Google, 75% of users who do searches do not surpass the first page of results[3] were taken into account. The objective was to know whether the material being consumed by readers has a medical basis or not, since, in the online environment, information is spread quickly and easily. In order to avoid contamination in searches for data influenced by the registration of the Google account, the search was carried out in an anonymous mode.

RESULTS

Regarding the search for "breast cancer" (*cancer de mama*), starting in 2010, it was observed that the highest volume and peak of research occurred in the month of October. In addition, as of 2013, there was a progressive increase in the volume of searches during the months prior to October and a drop thereafter. Another point observed is the growing trend that the number of surveys had over the years (Figure 1).

Regarding the search for "breast self-examination" (*autoexame de mama*), it was not possible to observe a trend between 2009 and 2012; however, in relation to the months of the year, it was possible to note that there was an increase in the volume of research starting in 2010. From 2014 onward, it was noted that the trend to peak and the highest volume of research occurred in the month of October and that, in terms of volume, it remained low in the other months of the years and suffered a sudden increase when October arrived, immediately following an abrupt drop.

Regarding the researches by "mammography" (*mamografia*), it was found a constancy in the research line during the analyzed years, with a peak in volume from 2013, also in the month of October. And, starting in 2013, the same trend found in the keywords "breast cancer" (*cancer de mama*) and "breast self-examination" (*autoexame* ***de*** mama) was also seen, which suffered an abrupt increase in the volume of searches before the month of October, with a drop after that month (Figure 2).

With regard to the sites, 26 different articles were analyzed, nine for "breast cancer" (*cancer de mama*), nine for "breast self-exam" (*autoexame de mama*), and eight for "mammography" (*mamografia*),

Figure 1. Evolution of research on "breast cancer" from 2009 to 2019.

which were found on the first page of Google. It was seen that 13 of them did not specify the author's name, 13 also did not contain the information of who was the technical responsible for the publications, and nine did not contain the references of the information disclosed.

It was also notorious that the sites with the greatest chance of getting hits due to being in higher rankings in the research are in the health area, but they are not from medical professionals, medical institutions or hospitals, nor even linked with the Ministry of Health (Tables 1, 2 and 3).

It is observed that the website of the Brazilian Society of Mastology appears in seventh place when searching for "breast self-examination" (*autoexame de mama*) and does not appear on the first search page for the words "breast cancer" (*cancer de mama*) and "mammography" (*mamografia*).

DISCUSSION

This study managed to present the seasonality on issues related to breast cancer, as well as the impact of the Pink October campaign on search engines.

Breast cancer is the type of cancer with the highest incidence in women in the world, accounting for 24.2% of all cases in 2018. It is considered the fifth cause of death from cancer, in addition to being the most common cause of death from cancer in females[4]. According to the José Alencar Gomes da Silva National Cancer Institute (*Instituto Nacional de Câncer José Alencar Gomes da Silva* – INCA)[5], it is estimated that, in the years 2020 to 2022, 66,280 new cases of breast cancer emerged in Brazil, making this the most prevalent type of cancer among women, with 29.7% of new cases per year[5].

Among the ways to obtain an early diagnosis, mammography is still the most effective instrument, although the number of women who undergo this examination is still small. Socioeconomic class, level of education, and household income are among the factors that influence the performance of this exam[6], and perhaps the low number of searches about breast cancer is a consequence of this lack of information.

Swedish cities that provide breast cancer screening report a 44% decrease in predicted mortality from the disease among women who are screened. In the United States, from 1980 onward, the numbers point to a decrease of 39%. In addition to contributing to a reduction in mortality, screening can contribute to adherence

Figure 2. Survey on "mammography" (*mamografia*) in most months, peaking in October and decreasing after that.

Table 1. Search results for "breast cancer" (*câncer de mama*).

	Websites	Author	Technical manager	Textual references	Type of website
1st place	https://www.inca.gov.br/	Not specified	Not specified	Without	Governmental
2nd place	https://www.minhavida.com.br	"Editorial writing"	Yes, oncologist	With	Health
3rd place	https://mulherconsciente.com.br	Not specified	Not specified	With	Health
4th place	https://www.tuasaude.com/	Gynecologist and Obstetrician	Yes, gynecologist and obstetrician	With	Health
5th place	http://www.oncoguia.org.br/	"Equipe Oncoguia"	Yes	With	NGO
6th place	https://www.pfizer.com.br/	Not specified	Not specified	With	Vaccines and Medicines Company
7th place	https://www.gineco.com.br/	Not specified	Yes	With	Health
8th place	https://www.einstein.br/	Not specified	Not specified	Without	Hospital
9th place	https://saude.abril.com.br/	Yes, columnist	Not specified	With	Miscellaneous

NGO: non-governmental organization.

to less radical treatments and reduce treatment costs, as a consequence of the diagnosis of lesions in less advanced stages[7].

In the internet age, social networks are the most important places for sharing interests, information, and personal experiences, overcoming daily space and time limitations. People with health problems use social media to increase their knowledge about their disease and its respective treatments, often considering online findings as their main means of information and disrupting the doctor-patient relationship[8]. When analyzing the relationship with breast cancer, online research on breast self-examination has the ability to provide incorrect and/or incomplete information, which can induce the reader to take wrong measures, resulting in damage to health or delaying the disease diagnosis[9,10].

Many contemporary scholars have called the present moment the "fake news era", in which erroneous information, whether generated intentionally or not, spreads quickly and may have the intention of causing harm. In the health area, they have been very common. To verify this, 131 articles were analyzed, which confirmed that the number of studies investigating health and misinformation grew over the years. Evidence was found that misinformation is abundant on the internet and more popular than correct information, consequently leading to fear, anxiety, and distrust in institutions that generate truthful content and in the population that consumes this type of information. In addition, most bad information is created by individuals with no institutional or official affiliation, which leads to questioning what readers understand as a reliable source of information[11].

In an analysis of 68 sites that had information about breast self-examination, it was found that 55 were commercial sites, of which 11 had adequate and complete content, 16 had partial content,

Table 2. Search results for "breast self-examination" (*autoexame de mama*).

	Si Websites	Author	Technical manager	Textual references	Type of website
1st place	https://medprev.online/	Not specified	Not specified	With	Convênio
2nd place	https://www.gineco.com.br/	Not specified	Yes	With	Health
3rd place	https://pebmed.com.br/	Gynecologist and Obstetrician	Yes	With	Health
4th place	https://drogariasantoremedio.com.br/	"Admin"	Not specified	Without	Drugstore chain
5th place	https://www.inca.gov.br/	Not specified	Not specified	With	Governmental
6th place	https://www.tuasaude.com/	Gynecologist and Obstetrician	Gynecologist and Obstetrician	Without	Health
7th place	https://www.sbmastologia.com.br/	Not specified	Yes	With	Health
8th place	https://www.youtube.com/	Nutritionist Channel	Not specified	Without	Miscellaneous
9th place	https://laboratoriosobrinho.com.br/	Not specified	Not specified	With	Clinical Laboratory

Table 3. Search results for "mammography" (*mamografia*).

	Websites	Author	Technical manager	Textual references	Type of website
1st place	https://altadiagnosticos.com.br/	Not specified	Not specified	Without	Laboratory
2nd place	https://saude.abril.com.br/	Yes, columnist	Not specified	With	Miscellaneous
3rd place	https://www.americasamigas.org.br/	Not specified	Yes	With	Civil Society Organization (*Organização da Sociedade Civil* – OSCIP) and Human Rights Promoting Entity
4th place	https://www.minhavida.com.br/	With	Yes	With	Health
5th place	http://www.oncoguia.org.br/	"Oncoguide team" (*Equipe Oncoguia*)	Yes	Without	NGO
6th place	https://drauziovarella.uol.com.br/	With	Yes	Without	Doctor
7th place	https://laboratorioexame.com.br/	Not specified	Not specified	With	Laboratory
8th place	https://www.msdmanuals.com/	With	Yes	Without	Health

NGO: non-governmental organization.

and 23 had inadequate and/or incomplete content. With regard to guidelines, one website said that self-examination has the ability to prevent breast cancer and nine said that it allows for an early diagnosis or that it is the best resource for initial diagnosis. Only four listed possible unfavorable effects related to self-examination as a methodology associated with early diagnosis[10].

In our study, the results obtained showed that even sites with high-quality content, such as INCA and others related to the health area, do not present the reference source or the authors who wrote the text, a fact that does not disqualify the material available to the public, which would, however, be further qualified if these sources were cited.

One study sought to evaluate Youtube with the keyword "breast self-examination" (*autoexame de mama*). Initially, 200 videos were selected, of which 33 were classified as useful by two physicians and 54 were classified as misleading. The videos that contained useful information had good reliability, quality, and content and, when compared to the others, were longer. Videos with questionable content were mostly posted by individuals and their views per day were higher than those with correct information, and the total number of views was also higher in the group of videos with erroneous information[12].

As for the existing fatalism in relation to cancer and the amount of information found about it in the virtual environment, different consequences may occur among patients who have different levels of education. In those with a lower level of education and greater exposure to information via medical and health websites, this exposure ended up increasing their suffering in relation to cancer, contrary to what occurred with patients with a higher level of education, for whom this exposure reduced their suffering. This difference can be explained by the fact that patients with a higher level of education had greater literary skills to filter the information they were faced with, as opposed to patients with a lower level of education[13].

In the study by Leite Netto[1], the women who participated in the research were treated in the city of São Paulo, which is a metropolitan city and state capital, a place where women frequently use digital media. This fact denotes a certain selection bias in the results presented.

The history of Pink October begins in the 20th century, when the famous pink bow, which became a symbol of this campaign, was launched. The movement began in the United States, when several states that had isolated actions in relation to breast cancer and mammography joined together and made the month of October the official month for the prevention of breast cancer. This movement achieved worldwide popularity and, in 2002, the first action related to Pink October took place in Brazil: the lighting of the monument *Obelisco do Ibirapuera*.

Our study was able to demonstrate the importance of the Pink October awareness campaign in Brazil, from 2009 to 2019. Through the graphics displayed, it is possible to analyze the trend of the occurrence of search peaks for words related to breast cancer in October, in addition to a growing line with regard to the volume of research on these words over the years, demonstrating that more and more research has been done on this type of cancer. Thus, it is possible to note the growing interest of the population in the early diagnosis of a public health problem and the importance of campaigns that will publicize the importance of screening and enhance the performance of mammography.

Like our study, research from Malaysia assessed interest in breast cancer screening from 2007 to 2018 using Google Trends. A significant increase in research was also seen during the month of October, which shows increased interest in monitoring and early diagnosis of breast cancer not only in Brazil, as well as demonstrates that this interest is also correlated with the Pink October campaign[14].

Another Brazilian work was carried out with the aim of evaluating the impact of cancer-related campaigns on the Brazilian population, not only using data obtained from Google Trends, but also analyzing prostate cancer. Their results showed that, although breast cancer is not the most prevalent type of cancer in Brazil, it is the one of greatest interest to the Brazilian population, with three times the number of researches in relation to prostate cancer[15].

This internet cancer research behavior is likely to be related to the Pink October and Blue November campaigns. This shows that such campaigns have the strong effect of influencing the population's interest in the topics and in carrying out screening tests, such as mammography, which is reflected in the increase in the search volume in the months in question, verified through the Google Trends tool[15].

The increased search for information leads to greater awareness among the population about certain types of diseases, as well as on how to prevent and treat them, but it also affects the public health system, with groups that are not at risk overloading the system. Pink October was a success for increasing the search for information and mobilizing knowledge about breast cancer[15].

This relationship between Pink October and mammography can be seen in a survey conducted from 2014 to 2016[16], which showed that, in these years, there was a significant increase in the total number of mammograms performed during the month of October when compared to other months of the year. This can be considered an indirect marker of the positive influence that the campaign exerts on society, in addition to being a reflection of the population's increased search for information about breast cancer.

The present study sought to assess in general terms the access to information about breast cancer, however, using Google Trends, it was not possible to quantify the number of accesses or the gender and age of those who performed such searches. This fact ends up limiting the assessment of the impact of this on breast cancer awareness and on the performance of self-examination and mammography, especially in the population for which these tools are recommended for screening for the pathology. Likewise, the quality of the information presented on the websites was not evaluated in terms of the form and updating of the information presented, but only regarding the description of theoretical references, authorship, technical responsible or possible body responsible for the website.

Our study was able to show the carelessness that many sites show in not specifying the authorship and reference of the material presented, making it necessary to improve the legislation on this subject. Presenting the authorship and bibliographic references only qualifies the content presented and is a procedure that should be used systematically in health-related websites. It is expected that new studies emerge to contribute to the theme, which can quantify and assess the number of searches on the internet about breast cancer, as well as the gender and age of those who carry out such searches.

CONCLUSION

Through our study, it was possible to demonstrate the importance of health campaigns in terms of population awareness. Pink October is a reflection of this, since most of the search peaks of the analyzed keywords and which were related to breast cancer occurred in the month of October. Thus, one can see the positive effect of this campaign to raise awareness among the population about breast cancer and its screening methodologies, such as self-examination and mammography, as people start looking for ways to get informed about the disease.

AUTHORS' CONTRIBUTION

D.S.: supervision, conceptualization, methodology, writing – review & editing.

N.O.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing – original draft, writing – review e editing.

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Clinic, pathologic and molecular landscapes in ultra-young women with breast cancer in the State of São Paulo: a real-world study

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ABSTRACT

Introduction: Breast cancer (BC) centers are increasingly attending "ultra-young" women (UYW) patients (≤ 30 years), who usually present aggressive tumors and face specific problems. **Objectives:** We aimed to examine a multicentric casuistic view, addressing clinicopathological and molecular characteristics of BC, as well as therapeutic measures and oncological outcomes. **Methods:** A retrospective multicentric observational study of UYW with infiltrating BC was carried out. The patients were treated between the period from January 1991 to December 2019. Clinical, epidemiological, morphological, molecular, therapeutic and outcomes data were collected from the charts. **Results:** A total of 293 patients were followed for a average period of 34.5 months. Nulliparity was referred by 204 women (75.5%), of whom 81 (37.1%) were overweight or obese. Positive family history in first-degree relatives was verified in 25 patients (10.1%). Only 30 patients underwent genetic tests, which revealed inherited pathogenic mutations in 12 of them (37.5%). Thirty-two (32) cases were classified as T_1 at diagnosis (10.9%), while "De novo" stage IV was found in 29 patients (9.8%). Mastectomy was performed in 175 women (70.2%), quadrantectomy in 46 women (18.4%), and mammary adenectomies in 28 women (11.2%), of which 149 cases were reported after neoadjuvant chemotherapy (56.0%). A total of 111 patients had at least one positive lymph node (47.4%). The rate of patients with estrogen receptor-negative was 32.7% and the rate of patients with Human Epidermal Growth Factor Receptor 2-positive (HER2-positive) was 25%. The frequency of Luminal A neoplasias was 16.6%, Luminal B/HER2- was 35.9%, Luminal B/HER2+ was 15.1%, HER2 overexpressed was 9.3%, and Basal was 22.9%. Taking into account the outcomes, 173 patients were alive without disease (65.7%); 23 patients were alive with any form of recurrence (8.7%); and 67 patients (25.4%) evolved to BC deaths. **Conclusions:** It was concluded that UYW with BC are commonly diagnosed at advanced stages, present adverse morphological and molecular parameters, and have unfavorable prognosis.

KEYWORDS: breast neoplasms; ultra-young women; prognosis; therapeutics.

INTRODUCTION

In recent years, there has been great interest in breast cancer (BC) in young women. Current epidemiological data suggest that a substantial number of young women is affected with this neoplasia, being BC one of the leading causes of cancer related to deaths in this age range[1]. These patients share some unfavorable biological characteristics, with more aggressive tumors, that are likely to be larger in size when diagnosed, and correlated with higher

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locoregional recurrence rate and lower survival[2-4]. Young women are often less likely to seek early medical assistance.

In this context, it is necessary clarify what it means the term "ultra-young" women (UYW), since the definition for young woman in BC scenario varies according to the literature[5]. Considering a specific age related to health problems, such as future reproduction, background mutational process, emotional distress and management dilemmas, we advocate a subdivision of young women with BC into three subgroups: young (< 40 years), very young (≤35 years), and ultra-young (≤ 30 years).

Specialized centers in BC are increasingly attending UYW. Nevertheless, crucial aspects of the disease in this age range remain controversial and deserve further investigation. Managing patients of this age range, using the knowledge required for older patients, has become more and more difficult. Given these facts, it is meaningful to increase our wisdom on BC in UYW. In this article, we have considered a multicentric casuistic view that has occurred in several BC Centers located in the State of São Paulo, through a retrospective research organized by Brazilian Society of Mastology, São Paulo Region. Clinicopathological and molecular characteristics of BC in this age group, as well as therapeutic measures and oncological outcomes were addressed.

METHODS

We conducted a retrospective multicentric observational study with consecutive female ultra-young patients with BC.

Population

Only patients with infiltrating breast carcinomas aged less than or equal 30 years were included.

Only nine of 23 collaborating centers, invited to participate in this study, sent the completed worksheets to join the research project as follows: Hospital Pérola Byington, Instituto do Câncer do Estado de São Paulo, Hospital Sírio Libanês, Clínica Prof. Alfredo Barros, Hospital de Câncer de Barretos, Faculdade de Ciências Médicas de Santos, Hospital Regional de Presidente Prudente, Hospital das Clínicas de Botucatu and Instituto Arnaldo Vieira de Carvalho.

Data collection

All patients were treated between January 1991 and December 2019. The following data were recorded: age, body mass index, parity, hormonal contraception use, history of breast/ovarian cancer in the family, pathological tumor category, clinical staging, neoadjuvant and adjuvant treatments, type of surgery, number of positive lymph nodes, multicentricity/multifocality, presence of absence of peritumoral vascular invasion (PVI), histological grade (HG), nuclear grade (NG), and stage categorized according to the American Joint Committee on Cancer (AJCC) staging system.

Immunohistochemical information on estrogen receptor (ER), progesterone receptor (PgR), HER2 and Ki-67 protein were obtained from percutaneous biopsy and/or surgical specimens of patients diagnosed with the disease. ER and PgR were considered positive when the percentage of immunoreactive cells was equal or greater than 1%. The positivity for HER2 was defined as 3+ staining pattern, or gene amplification by Fluorescence in situ hybridization (FISH). Ki-67 protein was expressed in percentage of stained cells. The assessments were made by the local pathology laboratory in accordance with American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) recommendations.

We have classified the cases into five molecular subtypes, akin to modified recommendations of St. Gallen Consensus (2013)[6]:

- Luminal A-like: ER+ (≥ 10%), PgR+ (≥ 10%), HER2-, Ki-67 ≤ 20%;
- Luminal B-like HER2-: ER+ (≥ 10%), HER2-, PgR (<10%) or Ki-67 ≥ 20%;
- Luminal B-like HER2+: ER+ (≥ 10%), HER2+, any Ki-67, any PgR;
- HER2 overexpressed: HER2+ non luminal (ER < 10%);
- Triple negative: ER- (< 10%), PgR-(< 10%), HER2-.

Statistical analysis

Frequency of parameters were estimated. Statistical analyses were performed using a 0.05 P-value, calculated by the χ^2 test. The software IBM SPSS Statistics 25 was used for the analysis.

Ethical aspects

The research protocol was approved by the Ethics Committee of the Hospital Pérola Byington, which was managed by the Study Coordinator Center (number 3.001.256), and later approved by the Committees of the Collaborating Centers. An informed consent waiver was approved for all anonymous data retrospectively collected.

RESULTS

The population-based study included 293 patients up to 30 years old — that is, patients between the ages of 19 and 25 years (mean age = 27.3; median = 28). It shows the distribution of age at diagnosis in three categories as shown in Figure 1: 19–20, 21–25 and 26–30 years. They were followed by a median time of 41.5 months (1.5–207.0), with a median time of 34.5 months.

Body mass indexes are shown in Table 1. It is worth to point that 37.1% of the patients were overweight or obese.

Taking into consideration the reproductive factors, it was informed that 41.3% of the patients were current or past users of hormonal contraceptive (data available from 237 patients). Nulliparity was referred by 204 women (75.5%); parity 1–2 by 64 women (22.9%); and parity 3–4 by 28 women (10.3%) (data available from 207 patients).

We were able to collect data about family history in 246 cases. Positive family history in first-degree relatives was verified in 25 patients (10.1%), of whom 21 informed the corresponding relative's age at diagnosis: ≤30 years in two patients (9.5%); > 30 and ≤ 40 years in 10 patients (47.6%); > 40 and ≤ 50 years in 5 patients (23.8%); and > 50 years in 4 patients (19.0%). A total of 66 patients (26.8%) reported a family member with BC. Only thirty-two patients (10.9%) underwent multigene panel testing, of whom inherited pathogenic mutations were found in 12 of them (37.5%).

It is known that in most of the younger women the diagnosis is done by finding a lump. Remarkably in this casuistic view, locally advanced tumors were detected in 54.3% of cases. Detailed information about tumor sizes at diagnosis were listed as shown in Table 2. Clinical axillary lymph nodes evaluation in 283 cases revealed: N_0 in 99 cases (34.9%); N_1 in 121 cases (42.7%); N_2 in 53 cases (18.7%); and N_3 in 10 cases (3.5%). Clinical staging is showed in Figure 2, being evident high frequency of later stages. Twenty-nine patients presented systemic metastases and were classified as "De novo" stage IV (9.8%). The metastases sites were: bone — eight cases (27.5%); lung — five cases (17.2%); liver — four cases (13.7%); and multiple — 12 cases (41.3%).

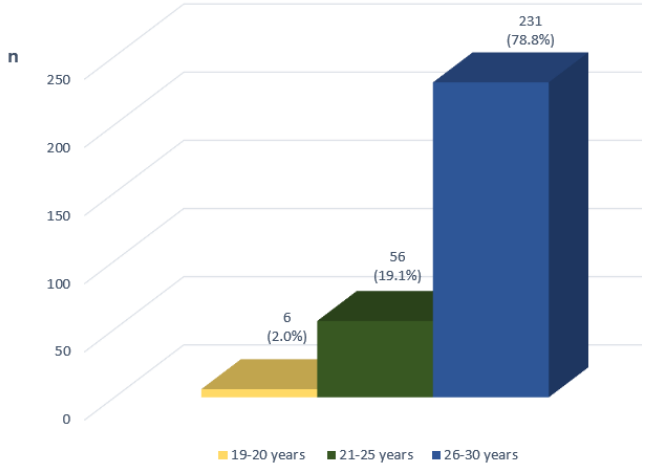

Figure 1. Age ranges of the 293 ultra young patients.

Table 1. Body mass indexes*.

Age range		n	%
< 18.5	underweight	21	9.6
18.5–< 25	normal	116	53.2
≥ 25–< 30	overweight	53	24.3
≥ 30	**obese**	**28**	**12.8**

*Without information: 75.

Table 2. Tumor size at diagnosis*.

	n	%
T_1	32	11.8
T_2	92	33.9
T_3	86	31.6
T_4	**62**	**22.7**

*Without information: 21.

Among 266 patients with attainable information, 149 of them (56.0%) received neoadjuvant chemotherapy, of whom 118 (79.1%) presented favorable clinical response (partial or total). In our study no patients underwent neoadjuvant hormone therapy.

Of all the types of local surgery performed in 249 patients with available data, mastectomy was performed in 175 patients (70.2%); breast conservative surgery was performed in 46 cases (18.4%); and unilateral or bilateral mammary adenectomies was performed in 28 patients (11.2%), as shown in Figure 3.

Sentinel node biopsy was performed in 78 patients (27.5%), and axillary dissection was made in case of involvement, and 205 were treated with up-front lymph node axillary dissection (72.4%). Information on lymph nodes involvement was obtained from 234 patients and Table 3 discriminates the results. It is worth mentioning that about half of the patients received neoadjuvant chemotherapy, likely generating interference in these findings.

Reliable information about morphologic neoplasia subtype were obtained in 260 cases. Invasive carcinoma (N_0s) was observed in 243 patients (93.4%), infiltrative lobular was extremely rare, being found in three patients (1.5%), and other subtypes were seen in 14 patients (5.3%).

Tables 4 and 5 shows, respectively, histopathological and immunohistochemical characteristics found in percutaneous biopsies before neoadjuvant chemotherapy or in the surgical specimens of the 192 patients of whom it was possible to obtain detailed information to classify the tumors in molecular immunohistochemical subtypes, as formerly systematized (Table 6).

Information about complementary radiotherapy was retrieved in 246 patients, most of them (179) received the treatment.

As previously reported, 149 women (50.8%) underwent neoadjuvant chemotherapy, 104 women (35.4%) received adjuvant chemotherapy and palliative chemotherapy was prescribed (4.4%) in 13 cases. Hormonal adjuvant, on the other hand, was prescribed in 159 women (54.2%).

Oncological outcomes are exhibited in Figure 4, unfortunately standing out the elevated contingent of BC-related deaths.

DISCUSSION

Breast Cancer in UYW represents a new challenge for physicians, who should be updated on modern biological concepts and latest recommendations for management. A more aggressive tumor behavior has been reported, and ultra-young patients are facing it with family and professional problems, as unique quality of life issues, including loss of fertility, contraception, pregnancy, sexuality, cancer during pregnancy, body image and emotional distress, all of them make the decision to do the treatment complicated[7].

A new era of classification criteria has been inaugurated and the term ultra-young come into use. We believe that it is a watershed, but not without constraints, since we consider that defining ultra-young women as those who are 30 years of age or younger would be more useful in clinical practice, as likely they share distinct biological and social particularities. For example, Cancello et al. observed more aggressive cancer phenotypes in women under 30 years, with approximately 75% of poorly differentiated lesions, compared with 55% in the group aged 30–34 years[8].

Patients under 35 years are known to have a higher rate of locoregional and distant recurrences, entailing elevated mortality.

Several studies have focused on specifically BC in ultra-young patients, and almost all studies show a worse prognosis[8-14]. According to Han et al. the risk of death has increased by 5% with a 1-year age reduction for patients <35 years.[15]

The most striking result that came out from our data is that, although a relative short-interval follow-up, 25.4% of the patients evolved to death caused by BC. Xiong et al. at the MD Anderson Cancer Center, in a landmark paper of outcomes in patients diagnosed with BC before the age of 30 years, revealed 5-year overall survival rates of 87% for stage I disease; 60% for stage II, 42% for stage III, and 16% for stage IV[12]. The strength of these results is the impact of late diagnosis in patients portending a worse prognosis due to the tumor aggressiveness.

Hankey et al. highlighted that 0.6% of the BC cases were diagnosed in women aged < 30 years in the USA in the 1990s (around 1,200 new cases per year)[16]. In the recent years there has been an increase in the cases of BC in young women[17-19], leading to an excessive number of loss of lives.

Regrettably, young women tend to be diagnosed at advanced stages, reflecting decreased awareness, lack of screening and fast-growing tumors. Most young patients are diagnosed with a palpable mass. Sole 11.7% of our patients presented small T_1 lesions at the beginning of treatment. At this moment, for a reasonable conjecture, strategies of awareness, and clinical and self-examinations should be implemented in the phase of life when mammography is contraindicated. Obviously, at least for patients with family history of BC, tailored screening measures should be adopted, including echography and magnetic resonance imaging. Moreover, healthy lifestyle should be adopted for every young woman. Indeed, we found out that almost 40% of our patients presented disproportionate body max index.

Genetic testing in young woman with BC is strongly recommended regardless of the family history. It is noteworthy that the chance of carrying a germline BRCA 1/2 mutations is at least 10% in young patients with BC, which is enhanced with a positive

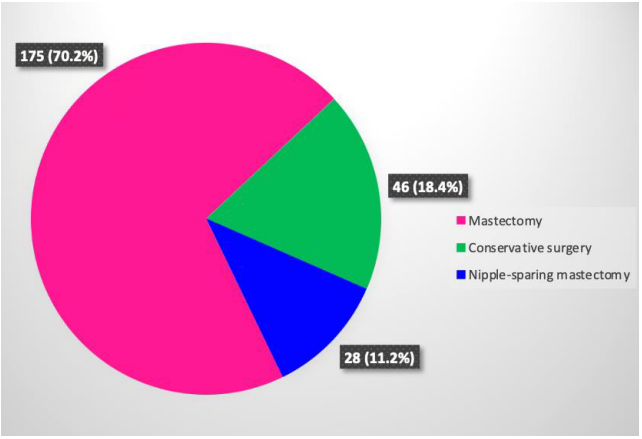

Figure 3. Types of local surgery performed in 249 patients.

Table 3. Frequency and extension of axillary lymph nodes infiltration in 234 patients with available data*.

	n	%
0	123	52.5
1–3	59	25.2
4–10	37	15.8
>10	**15**	**6.4**

*Without information: 59.

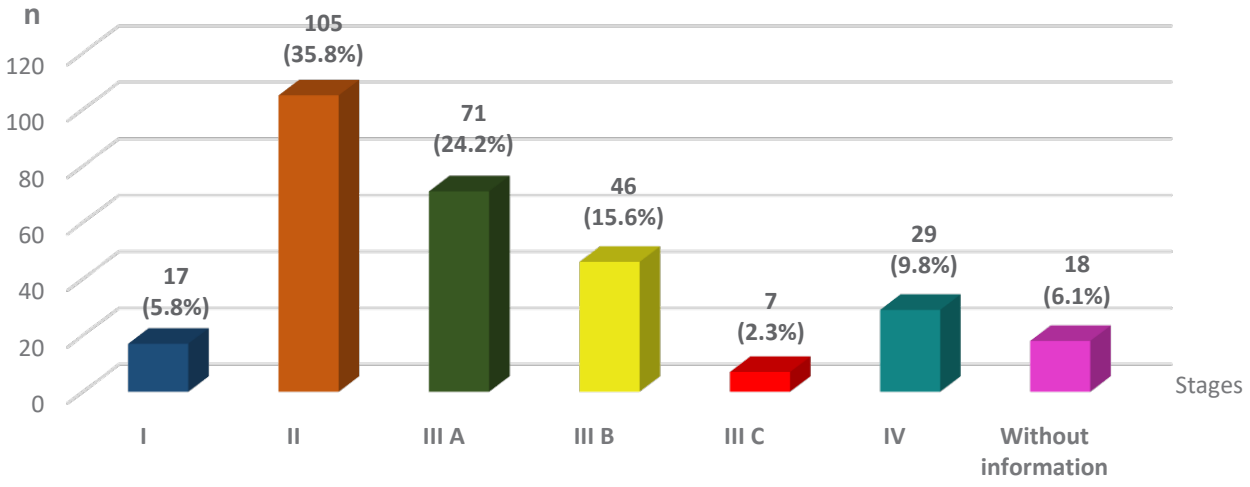

Figure 2. Clinical staging.

Table 4. Histopathological tumor characteristics.

	n	%
pT		
≤ 2 cm	84	28.6
> 2–≤ 5 cm	76	26.0
> 5 cm	52	17.8
complete tumor regression	25	8.5
without information	56	19.1
Histological grade		
I	9	3.0
II	139	47.5
III	109	37.2
without information	36	12.3
Nuclear grade		
1	4	1.4
2	92	31.3
3	165	56.3
without information	32	11.0
Vascular-lymphatic invasion		
Yes	72	24.5
No	155	53.0
without information	66	22.5
Multicentricity/multifocality		
Yes	31	10.5
No	219	74.8
without information	**43**	**14.6**

Table 5. Immunohistochemical characteristics.

	n	%
ER		
+	191	65.2
-	93	31.8
without information	9	3.0
PgR		
+	168	57.3
-	115	39.2
without information	10	3.4
HER 2		
+	68	23.2
-	203	69.2
without information	22	7.5
Ki-67		
≤ 20%	70	23.9
20%	180	61.4
without information	**43**	**14.7**

family history[20]. In cases of negative ER and/or high-grade tumors, the probability reaches 30%. Nevertheless, genetic testing is not available in the Brazilian public health system and its access is also limited in the private healthcare system[21]. Apart from BRCA 1 and 2 mutations, it is important to remember that BC is one of the most common cancer diagnosed among TP53 mutation carriers (Li-Fraumeni syndrome), and its peak of incidence is under 30 years[22]. In our casuistic view, only 32 cases underwent genetic testing, but predisposing hereditary mutations were identified in 12 patients (37.5%). Despite the small number of tests, a strong relationship between hereditary background and BC in UYW was observed.

Due to large tumor size and the immunohistochemical subtyping, more than half of the cases herein described was managed by neoadjuvant treatment (chemotherapy with HER2- targeted therapy when indicated), that entails that a downsizing and a possible complete response could establish a reliable surrogate marker for disease-free survival[23]. Almost 80% of our cases presented good clinical response (partial or total).

Ideally, the objective of local surgeries in BC therapy is the complete removal of the malignant cells. In practical terms, it is not totally possible, and there are three main options to be personalized for ipsilateral operation: quadrantectomy, mammary adenectomy and mastectomy, often followed by oncoplastic manoeuvres for partial or total reconstruction.

Many case series have found out that young patients have higher locoregional recurrence rates, which could result in decreased overall survival[24-26]. For Beadle et al.[24], the best locoregional control was achieved by patients with stage II disease who underwent mastectomy with radiation. Nevertheless, Cancello et al.[8] showed that the type of surgery performed did not influence

Table 6. Molecular breast cancer subtypes frequency*.

	n	%
Luminal A-like	32	16.7
Luminal B-like/HER 2-	69	35.9
Luminal B-like/HER 2+	29	15.1
HER 2 overexpressed	18	9.4
Basal like	**44**	**22.9**

*Without information: 101.

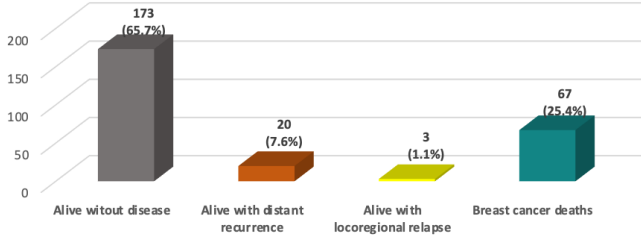

Figure 4. Oncological outcomes in 263 patients with appropriate follow-up information.

the rates of locoregional relapse. A metanalysis with more than 22,000 young patients (≤40 years) demonstrated that quadrantectomy and whole-breast radiotherapy provide overall survival control similar to mastectomy[27].

There is a concern if these conclusions are valid for UYW and for all molecular subtypes, but we are aware that the prognosis of young woman undergo breast-conserving surgeries have significantly improved compared with two decades ago, as seen by Botteri et al.[28]. Probably, this progress is owing to the policy that younger women do not have smaller volumes of breast tissue removed for cosmetic reasons (clear margins is mandatory), more accurate selection for breast conservation (tumor size, genetic testing and magnetic resonance imaging), and the anti-HER2 therapy implementation. Despite these facts, the most of the very young women continue to undergo any form of mastectomy worldwide. The arguments underpinning this conduct in very young patients are: higher risk of heritable abnormalities; more frequent local recurrences; greater life expectancy; higher mortality rate; and the paramount own patient's preference. In general, it seems to be a doctor-patient preference for mastectomy or mammary adenectomy.

The possibility of contralateral prophylactic adenectomy should be considered and accepted to individual practice. There is currently a widespread feeling in favor of bilateral mammary adenectomy in woman aged ≤ 35 years, reflecting a modern trend[29-31]. While its role is generally accepted in woman with mutated high-risk predisposing genes, Teoh et al. questioned the benefits in women who are just young at presentation or those who have a strong family history, but without demonstrable genetic mutation[32]. They suggest a multidisciplinary tailored approach to support individuals in a shared decision-making process.

Lymph nodal metastases are common in this age range. Ben Abdelkrim et al.[9], and Alipour et al.[33] observed involvement in 50% and 62% of women aged less than 25 years, whereas we noticed 47.5%. The extension of regional nodes excision should be elected case-by-case.

Our pathological findings were equivalent to those of other case series[9,10,34,35]. The most of our cases were represented by invasive carcinoma (no special type), and infiltrative lobular was very rare. Signals of neoplastic quiescence, such as histological grade I and nuclear grade I, were seen only in 3.5% and 1.5%. On the other hand, unfavorable immunohistochemical results were common. Negative ER status was observed in almost one third of the patients; negative PgR, in almost 40%; and Ki-67 > 20% was impressively common, being identified in more than 60% of the tumors. A Brazilian study, conducted by Bocchi et al., showed Ki-67 > 30% in 45.5% of the patients < 44 years and in 27.6% of women ≥ 44 years, and HER2 overexpression in 23.3% and 16.8%, respectively, in the same age rangers[34]. For us, HER2 positivity was detected in 25.0% of the cases with available information.

Breast Cancer is a heterogeneous disease, with several molecular intrinsic subtypes[36]. Basal-like (triple-negative) is more common in young patients, being more likely to be high-grade, and presenting also in this age a worse prognosis[37]. HER2-enriched subtypes, formerly showed poorer outcomes, currently, with HER2 directed therapy, are often associated to better recurrence-free survival. Our case series evidenced high frequency of luminal B and basal-like tumors, and low frequency of luminal A tumors.

An unfavorable landscape was observed in UYW with BC. We found high rate of advanced disease, with adverse pathological and molecular prognostic factors, a few genetic testing and high mortality. BC in young women is an important public health problem, more frequent in Latin American countries than in the USA, with dramatic consequences, as stated by Fidler et al.[38].

This research has raised many questions which need of further investigation. For changing the present-day scenario, we first need to educate the population, enhancing BC awareness and self-body attention since adolescence, and stimulating the adoption of a healthy life style[39]. In the study of Ogawa et al., about a breast self-examination in Japan, the average size of tumor was 2.5 cm at diagnosis for who performed it monthly, compared to 3.5 cm for those who did not[40]. A shift of this size is expected to result in a survival difference of at least 15%[39]. Self-examination practice in young women who did not undergo mammographic screening merits deeper consideration. On the other hand, appropriate and more efficient therapy is needed, taking into consideration modern strategies of precision therapy to improve outcomes. Tailored treatments offered by committed and skilled multidisciplinary teams are crucial to achieve the best holistic results when caring for the youngest women with BC.

AUTHORS' CONTRIBUTIONS

A.M.: Formal Analysis, Project administration, Software.
A.Y.: Formal Analysis, Project administration, Software.
C.F.: Investigation, Data curation.
E.P.: Investigation, Data curation.
F.A.: Investigation, Data curation.
G.T.: Investigation, Data curation.
H.V.: Investigation, Data curation.
K.C.: Investigation, Data curation.
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J.B.: Investigation, Data curation.
J.F.: Investigation, Data curation.
L.G.: Investigation, Data curation.
M.P.: Investigation, Data curation.
R.V.: Investigation, Data curation.
T.D.: Investigation, Data curation.
V.Jr.: Investigation, Data curation.
A.B.: Conceptualization, Supervision, Writing — first draft.

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ORIGINAL ARTICLE
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Guidelines for the prevention of secondary lymphedema following breast cancer treatment: adhesion and associated factors

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ABSTRACT

Introduction: Lymphedema is the most feared complication that may take place after breast cancer treatment. With treatment progression, doubts have arisen regarding the real benefits of lymphedema prevention care, as well as of patient adherence to guidelines. **Objective:** In this context, the aim of this study was to assess patient adherence to preventive lymphedema guidelines and the distribution of sociodemographic, clinical, and treatment variables according to adherence to treatment. **Methods:** A cross-sectional study conducted at the Cancer Hospital III/INCA, Rio de Janeiro, Brazil, concerning patients with breast cancer undergoing surgical treatment with an axillary approach. Participants were questioned about assistance care performance, exercise-related care, and limb ipsilateral to surgery care. A descriptive analysis of patient demographic, clinical, treatments, postoperative complications variables, and main outcomes (adherence to the guidelines) was performed through a central tendency measure and data dispersion and frequency measures analyses. Differences between means were assessed using the Student's t-test, while differences between proportions were evaluated using the chi-square test. A significance level of 5% was considered for all assessments. **Results:** Of the 103 women included in this study, 89.3% adhered to assistance care, 61.2% adhered to limb care, and 42.7% performed exercise-related care. Women undergoing chemotherapy ($p = 0.030$) and axillary lymphadenectomy (AL) ($p = 0.017$) exhibited greater adherence to care. Non-white patients ($p = 0.048$) and those who underwent AL ($p = 0.025$) adhered to limb care more frequently. Finally, patients displaying lower education levels ($p = 0.013$) and those who underwent AL ($p = 0.009$) adhered more frequently to limb exercises. **Conclusion:** Patients adhered the most to assistance care and limb care compared to exercise practice. Patients undergoing chemotherapy displayed greater adherence to care and non-white patients adhered the most to limb care. Women who underwent AL displayed greater adherence to all types of care and those presenting lower education levels adhered more frequently to exercise guidelines.

KEYWORDS: breast neoplasms; lymphedema; physical therapy modalities; disease prevention.

INTRODUCTION

Breast cancer is the most frequent type of tumor in the female population. Over 2 million new cases were estimated worldwide in 2020, and 66,000 new cases have been estimated every year in the 2020/2022 triennium in Brazil[1,2]. The estimated 5-year survival rate of patients undergoing breast cancer treatment in Brazil is of 75.2% (73.9–76.5) from 2010 to 2014. Difficulties in accessing diagnostic methods and adequate treatment lead to the arrival of patients in more advanced stages of the disease and displaying worse prognoses[3].

Tumor staging represents an important breast cancer prognostic factor. Therefore, early diagnosis during initial staging can lead to greater cure chances and lower treatment-associated morbidity. However, diagnoses in Brazil are still regularly performed in more advanced stages, requiring more aggressive therapeutic approaches and resulting in increased morbidity and increased

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incidence of functional, emotional, and social sequelae, directly compromising patient's quality of life[4-6].

Lymphedema is the most feared complication in patients undergoing breast cancer treatment. This condition is manifested by the accumulation of water, proteins, and cellular products in the extracellular space due to lymphatic system insufficiency concerning lymph transport in the face of flow obstructions[7,8].

The prevalence of lymphedema in patients undergoing an axillary surgical approach ranges from 0.4% to 92.5% and incidence between 5.9% and 56.7%, depending on the adopted diagnosis criteria and time elapsed from surgery[9-11]. In a prospective cohort study carried out at the Brazilian National Cancer Institute (INCA-Brazil) concerning women undergoing axillary lymphadenectomy (AL), lymphedema incidence was reported as 17% in 2 years, 30% in 5 years, and 41% in 10 years[12,13]. Macedo et al.[6] performed an observational study comprising 933 women (73.2% submitted to sentinel lymph node biopsy [SLB], 15.4% submitted to SLB followed by AL, and 11.4% submitted to AL) and concluded that SLB represents an independent protective factor concerning complications, including lymphedema, when compared to AL[14].

The main risk factors for lymphedema development comprise the number of removed lymph nodes, drainage chain radiotherapy, chemotherapy infusion in the upper limb ipsilateral to surgical treatment, limb infection, high body mass index (BMI), advanced age, and having developed early postoperative seroma and edema[13,15-17].

Preventive lymphedema guidelines are provided by a multidisciplinary team[18], as increasing limb volume can interfere with daily activities, generating physical and emotional consequences and directly impacting patient's quality of life[19]. Some guidelines recommend the use of repellents against insect bites, as well as avoiding trauma, burns, blood pressure measurements, and the administration of injections in the limb ipsilateral to the surgery[10,20]. In addition, other guidelines also comprise caution regarding excessive exposure of the ipsilateral limb to the surgery to heat, limb overload use restrictions, and recommendations against performing rapid and repetitive movements with the ipsilateral limb, as these activities increase arterial capillary ultrafiltration, which may overload the lymphatic system[21].

The practice of upper limb exercises comprises another preventive guidance, as muscle contraction promoted during exercise stimulates lymphovenous limb pumping, increasing lymphatic angiomotricity and the recruitment of collateral lymphatic pathways[18,20,22,23].

With the oncological treatment and surgical technique evolution, doubts have arisen concerning the real benefits of lymphedema prevention care, as well as regarding patient adherence to these guidelines. Thus, the aim of this study was to assess patient adherence to preventive lymphedema guidelines and the distribution of sociodemographic, clinical, and treatment variables according to adherence to care.

METHODS

This assessment comprises a cross-sectional study carried out at the Cancer Hospital III/INCA, Rio de Janeiro, Brazil, and was approved by the INCA Research Ethics Committee under no. CAAE 68894017.6.0000.5274.

Women diagnosed with breast cancer who underwent surgical treatment with an axillary lymph node approach (e.g., AL or SLB), with at least 5 months of surgery, and were undergoing follow-up at the Cancer Hospital III at any cancer treatment stage were included. Patients below 18 years of age, presenting disease progression and difficulties in understanding questions, were excluded.

All patients undergoing the axillary approach (e.g., AL or SLB) are monitored by the physiotherapy service preoperatively and postoperatively (first day, 1 month, 6 months, and 1 year after surgery). In these consultations, patients receive preventive guidelines for lymphedema as a routine in the institution.

Patients scheduled for routine consultations at the institution's Mastology and Oncology clinics were recruited. All patients were approached and informed about the nature of the study, objectives, risks, and benefits and they signed a free and informed consent form. A questionnaire composed of closed questions was applied in a private environment by a trained professional, and evaluation of postoperative complications (pain, limited range of motion of the shoulder ipsilateral to the surgery, infection in the affected limb, and lymphedema) was performed. Data collection was carried out from July 2017 to February 2018.

The variables used for the analysis were patient sociodemographic data (i.e., age, skin color, education, marital status, occupation, social security link, and income), clinical data (i.e., surgical laterality, BMI, clinical staging, histological type, histological grade, and side of the tumor), and treatment data (i.e., breast surgery, breast reconstruction, axillary approach, chemotherapy, radiotherapy, hormone therapy, and target therapy), which were obtained from physical and electronic medical records.

Participants were asked about the following limb care: blood pressure measurements, injection applications, use of tight objects in the upper limb ipsilateral to the surgery, limb exposure to heat (e.g., oven, stove, hot packs, sauna, and hot tubs), cuticle removal from the hand ipsilateral to the surgery, limb protection against trauma, carrying out household tasks, performing upper limb home exercises, and load bearing by the upper limb ipsilateral to the surgery (the patient was asked if she supports, carries, pulls, or pushes heavy objects with her limb). The answer options for all questions were yes or no.

Preventive care was grouped into three categories, to better assess and understand the results, as follows:

- Assistance care: The patients were asked about performing blood pressure measurement and injections in the limb ipsilateral to the surgery. Negative responses to both questions indicated adherence;

- Limb care: The patients were asked about the use of tight objects in the upper limb ipsilateral to the surgery, limb exposure to heat, cuticle removal from the hand ipsilateral to the surgery, upper limb protection against trauma, and carrying out household chores. Positive responses regarding upper limb protection against trauma and negative responses for the other questions were categorized as care adherence;
- Exercise-related care: The patients were asked about the practice of home upper limb exercises and load bearing with the upper limb ipsilateral to the surgery. Positive responses to exercise practice and negative responses to limb load bearing categorized adherence.

Lymphedema was diagnosed through perimetry measurements performed on the day of the interview, measured bilaterally, using the elbow joint interline as the reference point. Limb circumference was measured every 7 cm above and below the interline, and limb volume was estimated using the truncated cone formula (Equation 1):

$$V = h \times (C^2 + c^2 + Cc)/12\pi \quad (1)$$

Where:
V: the volume and h is the distance between (C) proximal circumference and (c) distal circumference[24,25].

Lymphedema was considered when the difference between the volumes of the affected limb and the contralateral limb was ^{3} 10%.

The evaluation of other postoperative complications was performed as follows: pain (patients were asked about the presence or absence of pain at the time of evaluation); limited range of motion of the shoulder ipsilateral to the surgery (it was requested to perform active movement of the shoulder flexion and abduction; the patients who presented any functional deficit during the performance of the movements were considered to have limited movement and those who did not present a functional deficit were considered not limited); and infection in the affected limb (participants were asked about the occurrence of any episode of infection on the affected limb after surgery and whether they received antibiotic therapy).

A descriptive analysis of patient demographic, clinical, treatments, postoperative complications variables, and main outcomes (adherence to the guidelines) was performed through a central tendency measure and data dispersion and frequency measures analyses. Differences between means were assessed using the Student's *t*-test, while differences between proportions were evaluated using the chi-square test. A significance level of 5% was considered for all assessments.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 20.0 software.

Sample size was calculated considering 50% of all patients as adhering to preventive physical therapy guidelines at a significance level of 5%. These parameters indicated the inclusion of 96 women in the study.

RESULTS

A total of 103 women who underwent surgical treatment with an axillary approach for breast cancer were included in this study, with a mean age of 58.4 (+12.6). The mean time between the surgical approach and the conducted interview was 4.74 years (standard deviation 4.98), ranging from 5 months to 21 years.

Most women declared themselves white (55.3%), 79.6% presented over 8 years of education, 54.4% did not live with a partner, and 68.9% performed household activities as their main activity. Regarding nutritional status, 77.5% of women were classified as overweight or obese (Table 1).

Table 1. Sociodemographic, clinical, and treatment characteristics (n = 103).

Variables	Total N (%)
Age	
≤ 59	53 (51.5)
60	50 (48.5)
Skin color	
White	57 (55.3)
Non-white	46 (44.7)
Schooling, years	
≤ 8	21 (20.4)
8	82 (79.6)
Marital status	
No partner	56 (54.4)
With partner	47 (45.6)
Occupation	
Home occupation	71 (68.9)
Active occupation	32 (31.1)
Social security link	
None	44 (42.7)
Linked	59 (57.3)
Income	
< 1 minimum wage	43 (41.7)
1–3 minimum wages	47 (45.6)
> 3 minimum wages	13 (12.6)
Surgical laterality	
Nondominant	48 (46.6)
Dominant	50 (48.5)
Bilateral	5 (4.9)

Continue...

Table 1. Continuation.

Variables	Total N (%)
BMI	
Adequate	18 (22.5)
Overweight	26 (32.5)
Obese	36 (45.0)
Clinical staging*	
Initial (0, I, IIA)	29 (37.2)
Advanced (IIB, IIIA, IIIB, IV)	49 (62.8)
Histological type*	
Invasive ductal carcinoma	91 (89.9)
In situ ductal carcinoma	5 (4.9)
Invasive lobular carcinoma	3 (2.9)
Others	3 (2.9)
Histological grade*	
1	6 (6.5)
2	63 (67.7)
3	24 (25.8)
Tumor side	
Right	48 (46.6)
Left	50 (48.5)
Bilateral	5 (4.9)
Breast surgery	
Mastectomy	83 (80.6)
Conservative	20 (19.4)
Breast reconstruction	
Yes	31 (30.1)
No	72 (69.9)
Axillary approach	
Axillary lymphadenectomy	70 (68.0)
Sentinel lymph node biopsy	33 (32.0)
Chemotherapy	
Yes	88 (85.4)
No	15 (14.6)
Radiotherapy	
Yes	67 (65.0)
No	36 (35.0)
Hormone therapy	
Yes	82 (79.6)
No	21 (20.4)
Target therapy	
Yes	18 (17.5)
No	85 (82.5)

BMI: body mass index; *differences in values correspond to the lack of information.

Regarding clinical characteristics, most women (62.8%) presented advanced cancer staging (higher than IIB) and a histological type categorized as invasive ductal carcinoma (IDC) (89.9%). Regarding treatment, 80.6% of the patients underwent mastectomies, 68.0% underwent axillary lymphadenectomies, 85.4% underwent systemic treatment with chemotherapy, 65.0% underwent radiotherapy, and 79.6% underwent hormone therapy (Table 1).

Considering postoperative complications, 48.5% of all patients reported pain in the upper limb ipsilateral to the surgery at the time of the interview, 15.5% exhibited limited shoulder range of motion, 12.6% indicated they had already had at least one episode of limb infection, and 25.2% developed lymphedema (Table 2).

Regarding the implementation of preventive lymphedema guidelines, all interviewees claimed to have received the guidelines during the postoperative period. Considering adherence to guidelines, 89.3% of all patients adhered to assistance care, 61.2% adhered to limb care, and 42.7% performed exercise-related care (Figure 1).

When evaluating adherence to care-associated factors, women who underwent chemotherapy ($p = 0.030$) and AL ($p = 0.017$) exhibited greater adherence to care compared to those who did not undergo these treatments. Regarding limb care adherence, non-white women ($p = 0.048$) and those who underwent AL ($p = 0.025$) adhered more frequently compared to patients who did not undergo these treatments. Considering preventive care adherence through exercise, women presenting lower education levels ($p = 0.013$) and those who underwent AL ($p = 0.009$) adhered to exercise-associated guidelines more frequently (Table 3).

Table 2. Postoperative complications (n = 103).

Variables	N (%)
Pain	
Yes	50 (48.5)
No	53 (51.5)
Limited range of motion	
Yes	16 (15.5)
No	87 (84.5)
Affected upper limb infection	
Yes	13 (12.6)
No	90 (87.4)
Lymphedema*	
Yes	26 (25.2)
No	77 (74.8)

*There is 10% difference in volume between the upper limbs.

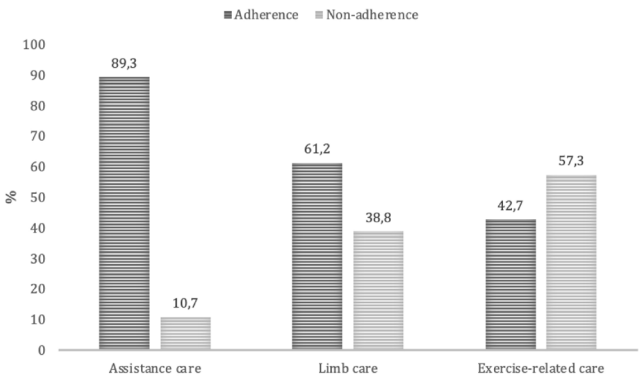

Figure 1. Patient adherence to preventive care of lymphedema guidelines.

DISCUSSION

The assessments carried out herein were performed concerning patients treated at a single breast cancer referral center. Although all patients reported having received preventive lymphedema guidance by the hospital's physiotherapy team on the first postoperative day and indicated that they understood its importance during the interview, only 89.3% of the patients adhered to assistance care guidelines, 61.2% to limb care guidelines, and 42.7% to exercise-related care guidelines. Adherence-associated factors were related to cancer treatment and patient demographic characteristics.

Despite the low adherence to exercise-related care, 74.8% of the patients did not present upper limb lymphedema, 48.5%

Table 3. Distribution of sociodemographic, clinical, and treatment variables according to adherence to care.

Variables	Assistance care			Limb care			Exercise-related care		
	Yes N (%)	No N (%)	p*	Yes N (%)	No N (%)	p*	Yes N (%)	No N (%)	p*
Skin color									
White	50 (54.3)	7 (63.6)	0.558	30 (47.6)	27 (67.5)	0.048	21 (47.7)	36 (61.0)	0.180
Non-white	42 (45.7)	4 (36.4)		33 (52.4)	13 (32.5)		23 (52.3)	23 (39.0)	
Occupation									
Home occupation	64 (69.6)	7 (63.6)	0.668	41 (65.1)	30 (75.0)	0.289	27 (61.4)	44 (74.6)	0.152
Active occupation	28 (30.4)	4 (36.4)		22 (34.9)	10 (25.0)		17 (38.6)	15 (25.4)	
Social security link									
None	38 (41.3)	6 (54.5)	0.401	31 (49.2)	13 (32.5)	0.095	23 (52.3)	21 (35.6)	0.090
Linked	54 (58.7)	5 (45.5)		32 (50.8)	27 (67.5)		21 (47.7)	38 (64.4)	
Schooling, years									
≤ 8	21 (22.8)	0 (0.0)	0.076	14 (22.2)	7 (17.5)	0.562	14 (31.8)	7 (11.9)	0.013
8	71 (77.2)	11(100.0)		49 (77.8)	33 (82.5)		30 (68.2)	52 (88.1)	
BMI									
Adequate	16 (22.8)	2 (20.0)	0.118	9 (18.4)	9 (29.0)	0.535	6 (18.2)	12 (25.5)	0.583
Overweight	20 (28.6)	6 (60.0)		17 (34.7)	9 (29.0)		10 (30.3)	16 (34.0)	
Obese	34 (48.6)	2 (20.0)		23 (46.9)	13 (42.0)		17 (51.5)	19 (40.4)	
Clinical staging									
Initial (0, I, IIA)	28 (38.9)	1 (16.7)	0.279	18 (39.1)	11 (34.4)	0.669	9 (27.3)	20 (44.4)	0.121
Advanced (IIB, IIIA, IIIB, IV)	44 (61.1)	5 (83.3)		28 (60.9)	21 (65.6)		24 (72.7)	25 (55.6)	
Surgical laterality									
Nondominant	44 (47.8)	4 (36.4)	0.662	28 (44.4)	20 (50.0)	0.630	17 (38.6)	31 (52.5)	0.342
Dominant	44 (47.8)	6 (54.5)		31 (49.2)	19 (47.5)		25 (56.8)	25 (42.4)	
Bilateral	4 (4.3)	1 (9.1)		4 (6.3)	1 (2.5)		2 (4.5)	3 (5.1)	
Breast surgery									
Mastectomy	73 (79.3)	10 (90.9)	0.360	52 (82.5)	31 (77.5)	0.529	38 (86.4)	45 (76.3)	0.200
Conservative	19 (20.7)	1 (9.1)		11 (17.5)	9 (22.5)		6 (13.6)	14 (23.7)	

Continue...

Table 3. Distribution of sociodemographic, clinical, and treatment variables according to adherence to care.

Variables	Assistance care			Limb care			Exercise-related care		
	Yes N (%)	No N (%)	p*	Yes N (%)	No N (%)	p*	Yes N (%)	No N (%)	p*
Breast reconstruction									
Yes	25 (27.2)	6 (54.5)	0.061	15 (23.8)	16 (40.0)	0.081	10 (22.7)	21 (35.6)	0.159
No	67 (72.8)	5 (45.5)		48 (76.2)	24 (60.0)		34 (77.3)	38 (64.4)	
Axillary approach									
Axillary lymphadenectomy	66 (71.7)	4 (36.4)	0.017	48 (76.2)	22 (55.0)	0.025	36 (81.8)	34 (57.6)	0.009
Sentinel lymph node biopsy	26 (28.3)	7 (63.6)		15 (23.8)	18 (45.0)		8 (18.2)	25 (42.4)	
Chemotherapy									
Yes	81 (88.0)	7 (63.6)	0.030	56 (88.9)	32 (80.0)	0.213	38 (86.4)	50 (84.7)	0.818
No	11 (12.0)	4 (36.4)		7 (11.1)	8 (20.0)		6 (13.6)	9 (15.3)	
Radiotherapy									
Yes	62 (67.4)	5 (45.5)	0.149	41 (65.1)	26 (65.0)	0.993	30 (68.2)	37 (62.7)	0.565
No	30 (32.6)	6 (54.5)		22 (34.9)	14 (35.0)		14 (31.8)	22 (37.3)	

BMI: body mass index; Values in bold indicate p<0.05; *p-value: the χ^2 test.

reported pain in the upper limb ipsilateral to the surgery at the time of the interview, and 15.5% exhibited limited shoulder range of motion, all symptoms directly related to overload and low limb exercise[26,27]. Sherman et al.[17] observed that guideline adherence increased from 79% to 86% from the first to the 6-month postoperative assessment and was maintained in the follow-up until 12 months after surgery. In this study, the mean time between surgical treatment and interview was 4.74 years.

Regarding care, adequate adherence (89.3%) was probably maintained due to an association between health professional conduct and more sporadic events, such as blood pressure measurements and punctures or injections in the limb ipsilateral to surgical treatment. The hospital unit where the study was carried out, being a reference hospital in the treatment of breast cancer, has a well-established routine regarding the nonperformance of these procedures in the upper limb ipsilateral to the surgery whenever possible[18,28].

In this study, most women presenting advanced clinical staging and underwent radiotherapy adhered to assistance care, albeit with no statistical significance. Statistical significances were observed only between this type of care and for patients undergoing chemotherapy. Studies have observed that both radiotherapy and chemotherapy present risks concerning lymphedema development[10,22,29-31]. In a Brazilian cohort followed at the same hospital unit, advanced breast cancer stage, lymphatic drainage chain radiotherapy, and chemotherapy administration in the upper limb ipsilateral to surgery increase the risk for limb lymphedema[13].

Concerning limb care, most patients followed the provided guidelines. Among patients who followed limb care, 76.2% underwent axillary emptying. According to the literature, patients who undergo AL display a higher risk of developing lymphedema compared to those who undergo SLB[10,14,32,33].

At present, significant doubts concerning the real need to follow so many preventive guidelines are in place, as well as which guidelines are in fact important, and which should be maintained. Some studies have not reported associations between ipsilateral upper limb volume increase and venipuncture surgery, injections, or blood pressure measurements performed in this limb[20,34]. Ferguson et al.[20] also reported no association between lymphedema and upper limb trauma. In contrast, when evaluating associations between lymphedema and infection, Fu[26] stated that women presenting upper limb infection are more likely to develop lymphedema, and Ferguson et al.[20] noted that infection increases risks for developing lymphedema. Other assessments have also reported significant associations between infection in the limb ipsilateral to surgery and lymphedema[12,31,35,36].

Regarding exercise-related care, over half of the patients (57.3%) reported not adhering to the recommended guidelines, bearing weight, and not practicing regular upper limb exercises. The literature reports that physical exercise has emerged as an important survival recommendation and important ally in lymphedema prevention. Upper limb exercise is an important

strategy in complex physical therapy as well as a useful tool in long-term lymphedema management. Exercise programs that include aerobic and resistance exercise do not trigger or exacerbate lymphedema[31,36]. In addition, there is a consensus that women who undergo surgical breast cancer treatment benefit from resistance exercise through physical function maintenance and recovery in the affected upper limb, as well as a healthy body composition[37,38]. Concerning patients who adhered to this type of care, most presented less than 8 years of education and had undergone AL, demonstrating greater adherence to exercise practice and care regarding weight bearing with the upper limb ipsilateral to the surgery.

Axillary lymphadenectomy is the most consistent risk factor for upper limb lymphedema following breast cancer treatment[12,13,31], which may explain the greater upper limb exercise adherence of the patients assessed in this study. Jammallo et al.[39] demonstrated that women who underwent AL presented greater postoperative fear compared to those who underwent SLB or who did not receive axillary surgery. Similar findings were also reported by McLaughlin et al.[7], in which persistent concern regarding lymphedema was reported by 75% of women who underwent AL and by 50% of those who underwent SLB at 12 months of follow-up.

Lu et al. carried out a clinical trial in which patients undergoing surgical breast cancer treatment were randomized to either only receive guidance on preventive lymphedema care or receive both physical therapy and limb care guidance, and also a control group, which did not receive any orientation or undergo physiotherapy. The patients were followed up for 1 year, and the authors observed that physical therapy associated with preventive care guidance displayed a 65% reduced risk of developing lymphedema, but did not observe any benefits concerning the exclusive guidelines for lymphedema prevention, justifying that the patients who received the guidelines only did not adhere to care and stating that poor adherence to self-care programs is capable of preventing treatment success.

This study has a limitation that needs to be considered. The research did not assess the relationship between adherence and surgery time in order to observe whether patients who operated more recently adhered more to the recommendations than those who operated many years ago.

Physical therapy aims to prevent possible postoperative complications and promote comprehensive care, aiming at better quality of life for the patients. To this end, all patients diagnosed with breast cancer must have access to a physical therapy routine, monitored during all cancer treatment stages, as well as in the follow-up period[18,40].

The physiotherapy team must be attentive to the way it presents preventive lymphedema guidelines, to generate more information and less patient anguish, consequently improving patient care. The physical therapy approach must always seek adaptations and never prohibitions, providing understanding and cooperation and sharing self-care responsibility with all patients.

Further studies should be carried out with a higher number of participants and considering Brazilian population characteristics, in order to understand which guidelines are in fact necessary and, thus, generate less patient anguish and limitations.

CONCLUSIONS

Although the patients evaluated herein stated that they received preventive guidelines for lymphedema, this study observed difficulties concerning adhesion to exercise-related care. The guidelines presenting the greatest adherence were those associated with assistance care and limb care. Despite the low adherence to exercise-associated care, 74.8% of the patients did not present upper limb lymphedema.

Patients who underwent chemotherapy presented greater adherence to care, and non-white patients adhered the most to limb care. Women who underwent AL exhibited greater adherence to all types of care and those presenting less education levels more frequently adhered to the guidelines for exercise-associated care for the upper limb ipsilateral to the surgery.

AUTHORS' CONTRIBUTIONS

E.A.N.F.: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing; F.O.M.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing; R.M.C.: Validation, Visualization, Writing – original draft, Writing – review and editing; M.B.A.L.: Conceptualization, Investigation, Methodology; L.O.M.: Conceptualization, Investigation, Methodology; S.S.A.: Formal analysis; A.B.: Formal analysis, Writing – review and editing.

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ORIGINAL ARTICLE
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Influence of the breast prosthesis volume in dose distribution in radiotherapy planning

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ABSTRACT

Introduction: The challenge of modern radiotherapy (RT) in breast cancer is to maintain its satisfactory oncological results, adapting to oncoplastic surgery and avoiding possible cosmetic damage. Considering that the breast prosthesis is not a target volume in RT planning, this study sought to analyze the effect of this volume on the coverage of the clinical target volume (CTV) of the breast. **Methods:** We performed a retrospective analysis of plans in 48 patients who submitted to RT in the first half of 2014. Two volumes were measured, such as breast CTV (breast tissue with the prosthesis) and real CTV (breast tissue excluding the prosthesis). The D95% values (dose that covers 95% of the volume) for each of them were verified and related to the volume of each one as well as the volume of breast prosthesis. **Results:** The analysis of the CTVs showed a significant difference between the mean volumes for the real CTV and breast CTV. While performing the CTV coverage, including the prosthesis, there is a perception that the dose covered 95% of the volume. Nevertheless, the analysis of the same plan after prosthesis volume exclusion revealed a difficulty in covering 95% of the breast tissue volume, indicating the interference of the prosthesis in therapy planning. Considering the dosimetric aspects, there were patients with real CTV values below the ideal dose of 47.5 Gy, after exclusion of implant volume. **Conclusions:** Our data reflected the volume of the prosthesis as an important variable that should be considered when planning adjuvant RT.

KEYWORDS: radiotherapy; breast neoplasms; breast implants; mammaplasty.

INTRODUCTION

Breast cancer (BC) is the most incident cancer with high mortality among Brazilian women. Globally, in 2018, it caused 670,000 deaths, of which 17,763 deaths were estimated in Brazil, including 17,572 women and 189 men[1,2].

Surgery, the conventional treatment for BC, has been evolving throughout the years. In the 19th century, Halsted[3] introduced the radical mastectomy, which was gradually replaced by the modified radical mastectomies with muscle preservation, developed by Patey[4] (1948) and Madden[5] (1972). In 1981, Veronesi et al.[6,7], followed by Fisher et al. in 1985[8], demonstrated that conservative treatment of BC followed by adjuvant radiotherapy (RT) had the same efficiency than that of mastectomy, considering overall survival rate. However, despite conservative treatment has been considered a conventional treatment (standard of care), the mastectomy still needs to be considered in many cases[8,9].

The introduction of plastic surgery techniques in oncology originated the term "oncoplastic surgery," aiming to integrate good oncological control, with favorable cosmetic results. Reconstructions are often used in postmastectomized women, including the insertion of breast implants, expanders, and autogenous tissues (i.e., TRAM, latissimus dorsi)[10,11]. This practice in mastology encompasses not only conservative treatments but also techniques involving immediate postmastectomy reconstruction, which can be either skin-sparing mastectomy type or nipple-sparing mastectomy[12,13].

RT can be considered as an adjuvant treatment option in patients with mastectomy. The indication for this treatment, called postmastectomy RT (PMRT), is based on the probability of local and regional failure in the case of isolated radical surgery[14]. Adjuvant RT can improve the rates of locoregional control, specific cancer survival, and also overall survival[15-18]. To perform the PMRT, prior planning is necessary in which the clinical treatment

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volume (clinical target volume [CTV]) is defined. CTV is the volume of tissue that may contain the microscopic disease and/or gross subclinical disease[19,20].

After defining the treatment volume, it is necessary to analyze the dose that will be absorbed by it, which is defined as the measure of the biological effects produced by ionizing radiation. This analysis is performed using the dose and volume histogram (DVH) and presents the ratio of absorbed dose per volume of analyzed tissue[21].

Most breast RT guidelines include breast implants as a treatment volume; however, breast implants are not a volume of interest for RT[22]. Considering that the prosthesis material does not contain tumor cells, the present retrospective study evaluated whether the dose distribution (D95%) in the CTV can be better evaluated by excluding the prosthesis volume in the calculation of the total volume to be treated.

METHODOLOGY

In this retrospective study, 48 plans of patients treated with RT in the first half of 2014 were evaluated. The inclusion criteria were as follows: women above 18 years, with breast reconstruction, and with the indication of RT (postmastectomy radiation). Forty-six patients had subcutaneous implants, while two patients had subpectoral implants. All cases were planned based on the three-dimensional conformal technique and, for each plan, the D95% values (dose covering 95% of the target volume) were analyzed for the breast CTV (breast tissue with the prosthesis) and the real CTV (breast tissue excluding the prosthesis). To exclude the prosthesis volume from breast CTV, we used the Boolean operation. The prescribed dose for all cases was 50 Gy in 25 fractions, with 6-MV linear accelerator beams. To avoid the buildup effect (the peripheric zone of the body where the radiation has some instability and the delivered dose is not uniform), we have used a Boolean operation to subtract a distance of 0.5 cm of skin.

Dose distribution was evaluated slice by slice of images, and DVH analysis was performed to ensure that recommended doses would cover 95% of the target volume (D95%). Based on the study by the Radiation Therapy Oncology Group 1005 protocol, 47.5 Gy was considered the ideal dose and 45 Gy was considered the acceptable dose for D95%[23].

All dose distributions were considered based on breast CTV, real CTV, and prosthesis volume, aiming to verify the correlation among them.

The planning used to calculate the treatment doses was Eclipse v. 8.6 (AAA, Varian Medical Services). For the analysis of statistical correlation between variables, nonparametric tests were used (t-test, Wilcoxon test, and Spearman's rho) and the established significance level was 95%.

Considering the retrospective and dosimetric characteristics of this study, it did not change the original prescriptions and doses delivered to the patients.

This study was approved by the Research Ethics Committee (11787219.5.0000.5437) of Barretos Cancer Hospital.

RESULTS

From the 48 analyzed plans, 27 plans corresponded to left breasts and 21 plans corresponded to right breasts. Figure 1 contains a representative image of CTV delimitation, showing the delineation of the created volumes of breast CTV (including the volume of the prosthesis), real CTV (excluding the volume of the prosthesis), and the volume of the prosthesis alone.

From the measured volumes of 48 patients, the mean, maximum, and minimum volumes of CTV values for the total (breast CTV) and real (real CTV) breasts were determined. The distribution analysis of measured volumes showed a significant difference between the mean volumes for the real CTV and the breast CTV, the latter being significantly higher (Figure 2A). The means of these values, as well as the mean value of the prosthesis, are shown in Figure 2B, which highlights the difference between real CTV and breast CTV ($p<0.001$).

The D95% values were determined based on measured volumes. The dose histogram and volume shows the dose distribution curve for the CTV for one randomly selected patient, containing the dose curve for the real CTV (orange) and the breast CTV (red), as shown in Figure 3A. It is possible to observe a shift of the curve to the left when the volume of the prosthesis is excluded for the calculation of D95%, indicating that the value of D95% for breast CTV is higher than for real CTV. The coverage of the breast shows the dose distribution over the reconstructed breast, as shown in Figure 3B. It is important to observe the two underdosage areas, one just below the skin (buildup effect, denoted by orange arrows) and the other in depth (intersection of the prosthesis with the chest wall, denoted by blue arrow).

These data are corroborated by the graph showing the distribution of points, with a significant increase in D95% for breast CTV (Figure 3C). The mean D95% values for breast CTV (red curve) and real CTV (orange curve) were 48.2 Gy (94.5% of the total dose) and 49.2 Gy (93% of the total dose), respectively (Figure 3D). There were no significant differences considering the prosthesis volume and laterality (left or right breast, $p<0.0001$).

Despite the mean D95% of the real CTV being within the ideal dose limits, considering the distribution of volumes for all patients, the values of the real CTV included points below the ideal dose of 47.5 Gy. Furthermore, it can be observed that there was a value of 44 Gy, below the acceptable dose of 45 Gy. These data reflect the importance of considering the exclusion of breast implants in the assessment of a conformational plan, which is a relevant dosimetric information.

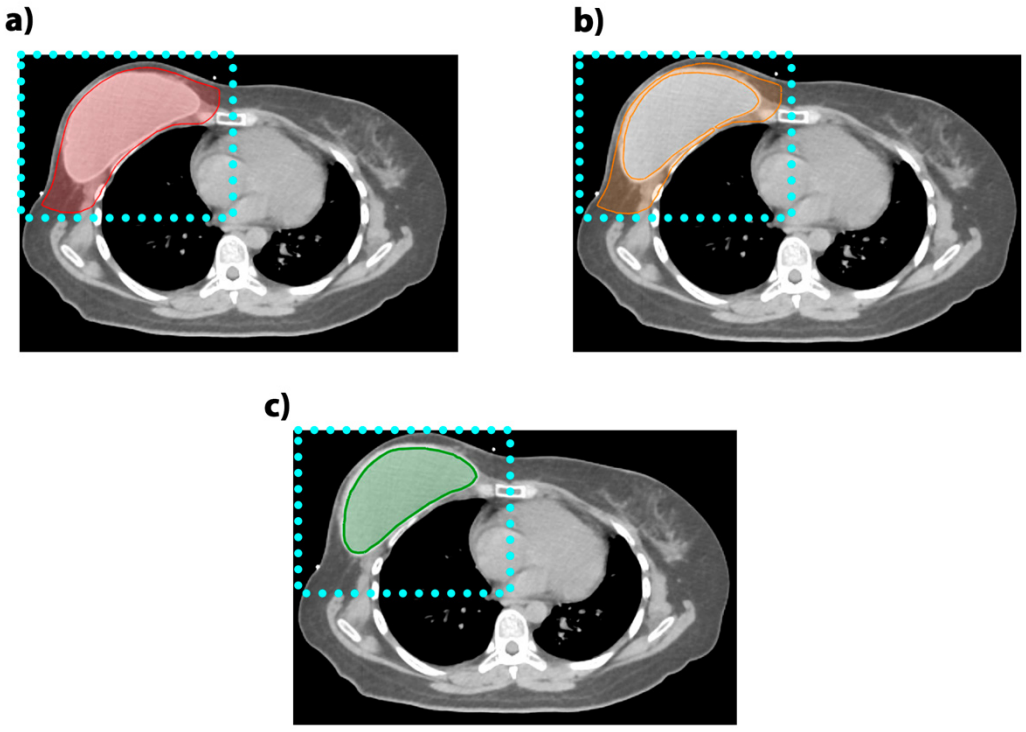
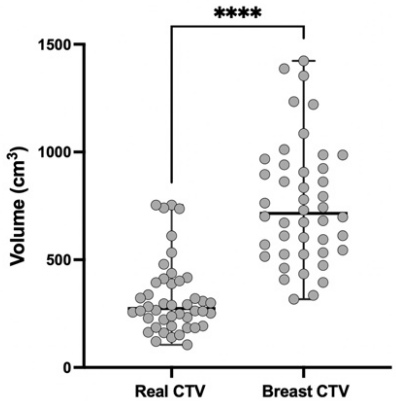


Figure 1. Delimitation of (A) total breast CTV (red area), (B) real CTV (orange area), and (C) prosthesis volume (green area). These volumes were designed for all patients in this study. The retraction observed right under the skin is due to the buildup effect zone.



b)

Calculated volumes for Real CTV, Breast CTV and Prosthesis (cm^3)			
	Mean	Maximum	Minimum
Real CTV	315,2	754	105
Breast CTV	750,3	1423	317
Prosthesis	434,5	821	104

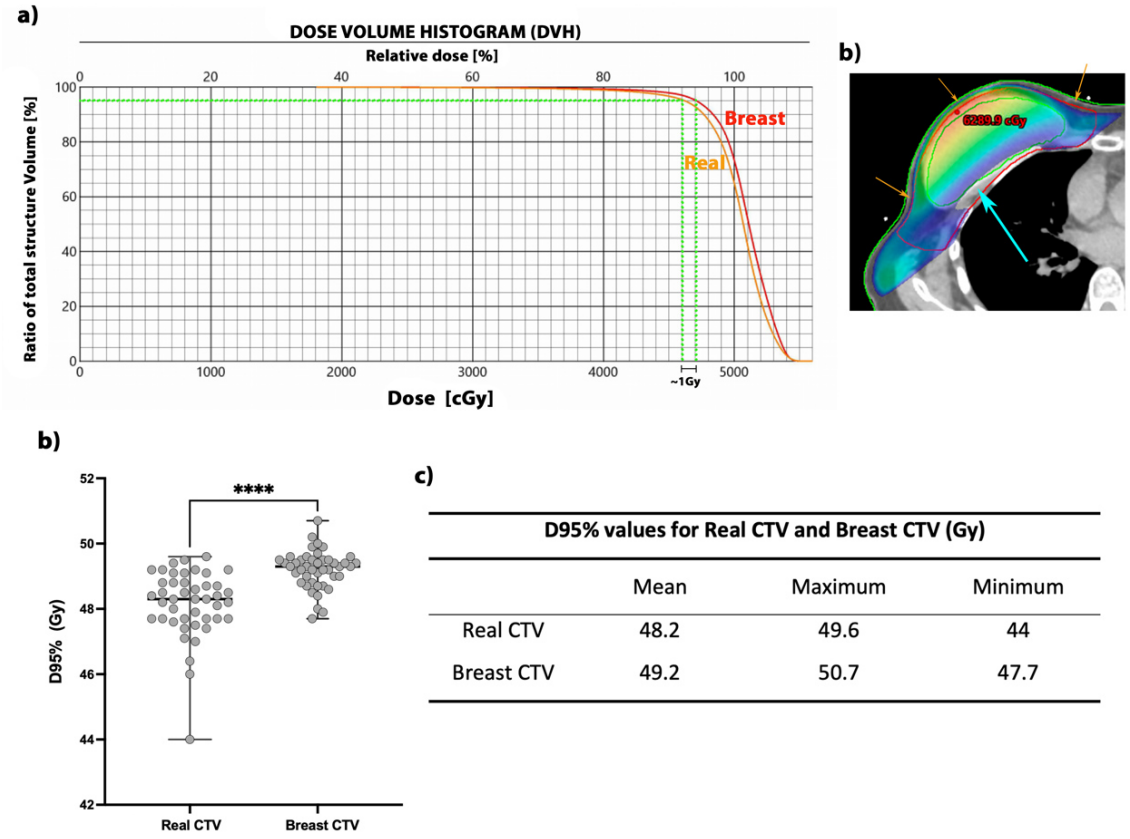
Figure 2. Influence of the prosthesis volume on CTV determination. (A) Graph showing the distribution of CTVs determined for real and breast CTVs, with a significant difference of volumes when considering prosthesis in the calculation of CTV. (B) Average, maximum, and minimum volumes collected for patients. P<0.0001.

DISCUSSION

Immediate breast reconstruction is an attractive procedure for patients undergoing mastectomy. Ideally included in the overall treatment of the patient, this practice brings the benefits of reducing psychological trauma, more favorable cosmetic effects, lower cost, and reduced morbidity related to surgery[24,25]. However, RT treatment after breast reconstruction may compromise the cosmetic effect[26,27].

Despite the impact of PMRT in breast reconstruction, this approach has been shown to be beneficial to patients, by preventing tumor recurrence[24]. The main goal, in this case, is to reduce the risk of locoregional recurrence, prolong the patient's survival, and reduce the secondary spread of the tumor[25].

Considering the PMRT in reconstructed breasts, the literature lacks information about the effect of the prosthesis in the planning and delivery of RT, which is a relevant factor considering the evolution of planning in RT[25]. The main focus explored in published papers is directed to organs at risk protect strategies, such as the heart and lung[25,28]. Other considered factors are



D95% values for Real CTV and Breast CTV (Gy)

	Mean	Maximum	Minimum
Real CTV	48.2	49.6	44
Breast CTV	49.2	50.7	47.7

Figure 3. Effect of CTVs on D95%. (A) Comparative graph showing the difference of D95% determined for the real CTV and breast CTV. (B) Curve of 50-Gy coverage for breast. The subdosage breast tissue areas are pointed out by the orange (under the skin) and blue (intersection of the prosthesis with the chest wall) arrows. Meanwhile, the prosthesis is almost entirely covered (area delimited by green area). (C) and (D) Mean, maximum, and minimum values were obtained for the real and breast CTV groups. P<0.0001.

the complications that lead to the need for excision and loss of the prosthesis[14]. Given this scenario, scientists have questioned whether RT after reconstruction would be the ideal approach, but a study presented by Allué et al. in 2019 showed that RT before reconstruction brought higher risks of failure when compared with patients who received the postreconstruction treatment[29].

Clinical results show that breast reconstruction can affect RT planning. In this context, an adequate and precise planning, which will be able to differentiate the real tissue that receives the RT dose, can be helpful for the reduction of problems related to PMRT. It is of critical importance for the radiation oncologist to assess the breast anatomy to define the residual breast tissue that may harbor microscopic cells. Depending on the placement of the tissue expander/implant in the prepectoral or subpectoral space, microscopic cells may remain anterior and/or posterior to the expander/implant. This is of even greater importance in the setting of close or positive surgical margins in the postmastectomy setting when dose distribution and assurance of adequate dose in the areas of greatest concern for microscopic residual may need to be factored into treatment planning. In such scenarios, bolusing of the skin to improve superficial dose and/or boosting in the postmastectomy setting may be considered. This analysis confirms that the inclusion of the prosthesis volume in dose coverage analyses may falsely indicate that adequate dose is being achieved. A more detailed DVH assessment excluding the prosthesis volume serves to better ensure adequate coverage of the true breast tissue at risk of harboring microscopic cells and may inform decisions regarding the need for bolus and/or boost to achieve coverage goals.

In this study, we demonstrated that the exclusion of the breast implant in the assessment of D95% in the target volume during RT planning can interfere with coverage, considering that the implant itself does not represent a target to be treated. The real CTV, excluding the prosthesis volume, showed a difference in the D95%, highlighting that the prosthesis/breast volume ratio can be a factor to overestimate the coverage of the target. The practical effect that this information reveals is that even though there is complete coverage of the area to be treated, the

D95% related to the actual CTV is actually lower, implying less coverage than necessary. Considering the dosimetric aspect, two regions of underdosage are expected—one just below the skin (buildup effect) and the other in depth (intersection of the prosthesis with the chest wall). This is a common effect in the 3D-RT technique and is related to the buildup effect (in the peripheric region), with the longer traveled radiation pathway in the depth zone. It is worth to mention that upon exclusion of prosthesis volume, those regions may become more evident.

Despite the mean value of D95% being within acceptable limits, we observed the values below 47.5 Gy, including one patient below 45 Gy. Thus, the exclusion of breast implants in the evaluation of a plan can be a relevant dosimetric information. Less number of patients and lack of correlation with clinical data are the limiting factors of this study, but the evidenced dosimetric implications can be valuable data for future clinical approaches. In this way, studies including a larger number of patients and correlating the dosimetric implications with the clinical effects in disease control and toxicity are necessary. Its application in clinical practice should be better investigated with studies to check whether this form of assessment interferes with local recurrence rates, overall survival, and specific BC.

CONCLUSIONS

In this study, we evaluated the influence of excluding the volume of the prosthesis in determining the CTV, and the effect reflected in the D95% values in patients with postmastectomy, with breast reconstruction and submitted to RT. Our data reflected the volume of the prosthesis as an important variable that should be considered when planning adjuvant RT.

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AUTHORS' CONTRIBUTIONS

P.V.F.: Data curation, Formal analysis, Methodology, Writing — original draft, Writing — review and editing. D.S.: Data curation. L.E.: Data curation. A.B.: Data curation. D.L.C.: Data curation. R.M.S.S.: Data curation. F.B.: Conceptualization, Data curation, Methodology. F.A.S.M.: Conceptualization, Data curation, Methodology. S.A.M.: Conceptualization, Formal analysis, Writing — original draft, Writing – review and editing. W.F.A.: Data curation, Formal analysis, Writing — original draft, Writing — review and editing. A.A.J.: Data curation, Formal analysis, Writing — original draft, Writing — review and editing. M.D.M.: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Visualization, Writing — original draft, Writing — review and editing.

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ORIGINAL ARTICLE
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Knowledge of basic attention professionals about prevention and early detection of breast cancer in the state of Goiás

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ABSTRACT

The role of Basic Health Care (BHC) professionals is essential in the primary and secondary prevention of breast cancer. The aim of this study was to characterize BHC professionals in the Health Regions of a federative unit and to assess their knowledge about breast cancer. This was a prospective study carried out with BHC professionals from the state of Goiás. Phase 1 – Preparation of material and training of the team. Phase 2 – Agreement of actions between executing team and coordination of health regions. Phase 3 – Presentation of project at the collegiate meeting. Phase 4 – Qualification of BHC professionals with different learning methods and application of questionnaires, evaluating the contribution of the action. A total of 1,133 professionals were included; mean age was 36.3 years, and they were predominantly women (87.6%), working as community health agents (59.2%) and at public service (76.3%). Only 53.8% of professionals identified the female sex as a risk factor for breast cancer, while 90% identified family history as an important factor for the development of the disease. Important changes in physical examination that can occur in patients with the disease, such as skin retraction, skin bulging and nipple injury, were mentioned as a risk factor only by 35.3%, 31.3% and 39.7%, respectively. BHC professionals who participated in the project had less than ten years of professional experience and significant restrictions of knowledge about primary and secondary prevention of breast cancer. They still experience difficulties in accessing mammography and specialized care.

KEYWORDS: breast neoplasms; primary prevention; community health planning; health education; health promotion.

INTRODUCTION

In Brazil, standardized breast cancer mortality rates between 1980 and 2016 ranged from 9.2 to 12.4 deaths per 100,000 women. This represents an increase of 33.6% in the period analyzed and reflects an upward trend in all regions of the country[1]. It should be noted that mortality rates are strongly related to access to health services and the quality of care offered to women with breast cancer[2,3]. Thus, one of the main strategies to improve morbidity and mortality is diagnosis in early stages of the disease[4].

Reducing mortality from breast cancer is one of the priorities of the National Policy for Comprehensive Women's Health Care, provided for in the National Plan for Primary Care[5]. Primary Health Care (PHC) is characterized by health actions, at individual and collective levels, covering health promotion and protection, disease prevention, diagnosis, treatment, rehabilitation, and health maintenance.

One of the foundations of PHC is the valuation of health professionals through encouragement and constant monitoring of their education and training as an essential strategy for the effectiveness of health education actions[5]. Prevention and early detection of breast cancer have been identified as essential and in need of intensification[6,7]. Thus, a scientific basis for health professionals involved in this process are necessary so that they can also assume an educational role and offer the population information that is useful for the prevention of breast cancer[8].

Strategies for health education actions must suit the profile of PHC professionals in each region. However, there is little information about the characterization of PHC staff in Federation Units. Another important matter is the lack of information about the experience of professionals in carrying out educational activities[9].

The aim of this study was to characterize the PHC professionals in the Health Regions of a Federation Unit and to assess

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their knowledge about breast cancer and the difficulties they face in daily practice.

METHODS

This was a prospective study whose target population was PHC health professionals of the state of Goiás. For this study, professionals involved in the early detection of breast cancer were considered to be the community health agents (CHA), the nurses and nursing technicians, physicians and mammography technicians.

The State of Goiás and Regional Health Boards

The state of Goiás is divided into 18 regional health boards according to the Master Plan for Regionalization. These boards intermediate the administration between the State Health Department (SES-GO) and the municipalities.

Methodology and Data Collection

This study was divided into four phases: planning of the executing team at SES-GO, creating strategies to raise awareness in the health regions; meetings with coordinators of health regions to agree on the actions to be developed by the project; presentation of the project for the health region at the collegiate meeting; conduction of a training course and application of semi-structured questionnaires with open and closed questions as a strategy for data collection.

Phase 1

The executing team planned the training activities, which involved the preparation of teaching material and data collection instruments, training of the working group to standardize pedagogical intervention strategies, awareness of the SES-GO coordination board on the importance of the participation of health professionals in the training course, preparation of a timeline of activities according to the number of professionals registered in each health region, and development of training activities.

Phase 2

Meetings were held with the coordinators of the regional health boards to agree on the actions to be carried out by the project, with representatives from the Mastology Program of Clinical Hospital of Universidade Federal de Goiás (HC/UFG), from the project "Liga da Mama", from the Faculty of Medicine, Nursing and Psychology at UFG, from the Association of Breast Cancer Patients, from the Regional Center for Nuclear Sciences of the Midwest, from the Superintendence of Sanitary and Environmental Surveillance of the State of Goiás, and from the Department of Sanitary Surveillance of Goiânia.

Phase 3

Presentation of the project at the collegiate meeting that takes place monthly under the organization of the regional health boards, where a representative of each city that makes up the board was present and all health actions to be carried out were defined.

Phase 4

On a date defined by the coordination of the regional health board and the project, as many health professionals as possible were transferred to the regional headquarters. Then, professionals were trained on a pedagogical approach with focus on health education. The pedagogical proposal adopted for this project was the methodology of problematization. This teaching method is based on the recipient's prior knowledge, which could be proven or reformulated during the theorization of information, in a way to provide them with instruments to intervene in the reality from which the problem was extracted[10].

The proposal of pedagogical intervention involves:

- Presentation of the team and proposal of the training course project;
- Integration technique with musical presentation;
- Application of a characterization questionnaire to health professionals;
- Discussion in small groups using guiding questions of a questionnaire addressing knowledge about risk factors, signs and symptoms, primary and secondary breast cancer prevention actions;
- Theoretical approach on risk factors, signs and symptoms and actions for primary and secondary breast cancer prevention, relating it to the information previously provided by the groups;
- Discussion in small groups to identify the difficulties and eases of health professionals for breast cancer prevention and early detection;
- Presentation of a summary by each group through a spokesperson;
- Workshops on self-examination with handling of the "Mammiga" Didactic Model and clinical examination of breasts;
- Assessment of the contribution of the training course to the practice of health professionals by means of a questionnaire.

Inclusion and exclusion criteria

All health professionals linked to the respective regional health boards of the state of Goiás were invited to participate in the study. Those who completed the training course and filled in the questionnaires in full were included. Professionals who did not accept to participate in the study were excluded.

Statistical analysis

The data collected were tabulated by double typing and analyzed using the Microsoft Excel program (Microsoft, Redmond, Washington, United States), version 2007. An exploratory analysis was performed using descriptive statistics and measures such as means, and absolute frequencies and percentages.

Ethical matters

This study is part of a line of research developed by the Brazilian Network for Research in Mastology, approved by the Research Ethics Committee of HC/UFG, under protocol number 037/2011. All good clinical practice recommendations by the National Health Council resolution nº 466/2012 and the Helsinki Convention were followed. All individuals invited and who agreed to participate in this study signed an Informed Consent Form.

RESULTS

The study included 1,133 PHC professionals linked to nine regional health boards in the state of Goiás. The mean age of professionals was 36.3 (± 9.8) years, ranging from 17 to 78 years. Women were predominant (87.6%), as well as CHA (59.2%), public-sector professionals (76.3%) and professionals with less than five years of training (37.0%). Other demographic and professional characteristics of the sample are described in Table 1.

Regarding risk factors for breast cancer, most professionals identified correctly the relevance of the female sex (53.8%), age (78.1%) and family history (90.0%). On the other hand, breast tenderness and breast cysts were considered risk factors for 47.7% and 58.0% of the professionals interviewed, respectively (Table 2).

Among changes in physical examination that can occur in patients with breast cancer, the presence of a nodule was reported by almost the entire sample (95.4%). Skin retraction, skin bulging and nipple injury was reported by 35.3%, 31.3% and 39.7%, respectively (Table 2).

Table 3 shows the difficulties and challenges experienced by PHC users and professionals in relation to the prevention and diagnosis of breast cancer (the percentage of access to consultations is high, in contrast to the percentage of access to the breast cancer screening exam, which is low; knowledge of the professional; body exposure; participation in educational groups).

DISCUSSION

This study is the result of a pioneering initiative in the state of Goiás encompassing individual and collective awareness, pedagogical intervention and professional training on various matters related to breast cancer. It identified demographic, professional, educational and assistance characteristics of PHC professionals in the state.

The characterization of professionals linked to PHC is fundamental for understanding some variables related to breast cancer screening and early diagnosis. The predominance of CHA in this study corresponds to the recommendations for the family health strategy, but the number of physicians who participated in the project was proportionally small compared to other professionals. This reflects the difficulty in training physicians and the low adherence to health education initiatives. This may be

Table 1. Characterization of health professionals included in the study (n = 1,133). Goiânia, Clinical Hospital, Universidade Federal de Goiás, 2020.

Questionnaire 1	n	%
Regional board		
Estrada de Ferro (Catalão)	69	6.1
West I (Iporá)	183	16.2
West II (São Luís de Montes Belos)	152	13.4
Serra da Mesa (Uruaçu)	138	12.2
North (Porangatu)	87	7.7
North surroundings (Formosa)	131	11.6
Northeast II (Posse)	90	7.9
Southwest I (Rio Verde)	161	14.2
Southwest II (Jataí)	122	10.8
Dados Pessoais		
Sex		
Female	992	87.6
Male	137	12.1
N/A	4	0.4
Ocupation		
Physician	15	1.3
Nurse	230	20.3
Community health agent	671	59.2
Other	210	18.5
N/A	7	0.6
Educational level		
Elementary School	17	1.5
Incomplete high school	46	4.1
Complete high school	636	56.1
Complete higher education	422	37.2
N/A	12	1.1
Postgraduate studies		
Yes	212	18.7
No	860	75.9
N/A	61	5.4
Situation		
Employed	1,067	94.2
Unemployed	34	3.0
Independent worker	8	0.7
Volunteer	5	0.4
N/A	19	1.7
Marital status		
Single	317	28.0
Married	580	51.2
Stable union	135	11.9
Separated	25	2.2
Divorced	63	5.6
Widow(er)	9	0.8
N/A	4	0.4

Continue...

Table 1. Continuation.

Questionnaire 1	n	%
Monthly income (in minimum wages)		
1 minimum wage	282	24.9
2 minimum wages	327	28.9
3 or more minimum wages	506	44.7
N/A	18	1.6
Religion		
Catholic	715	63.1
Protestant	326	28.8
Spiritist	50	4.4
Other	27	2.4
N/A	15	1.3
Professional data		
Tme since graduation		
< 5 years	419	37.0
5–10 years	335	29.6
> 10 years	307	27.1
N/A	72	6.4
Years of professional background		
< 5 years	399	35.2
5–10 years	355	31.3
> 10 years	321	28.3
N/A	58	5.1
Relationship with the institution		
Approved in public tender	864	76.3
Hired	222	19.6
Volunteer	33	2.9
N/A	14	1.2
Works somewhere else		
Yes	130	11.5
No	966	85.3
N/A	37	3.3

related to several factors such as inadequate remuneration, multiple working hours, quality of training offered and commonly used methodology[11]. There was also a predominance of professionals without complete higher education, which may have contributed to the unfavorable performance when it comes to theoretical knowledge about breast cancer.

In the last 15 years, the national regulations that define CHA's attributions started to prioritize operational activities, such as registering the local population to the detriment of educational, social and health promotion activities[5,12,13]. Many of these professionals experience limited access to specific training[14]. Thus, the work routine in primary health care in Brazil does not encourage

Table 2. Knowledge of health professionals about risk factors, prevention and diagnosis of breast cancer (n = 1133). Goiânia, Clinical Hospital, Universidade Federal de Goiás, 2020.

Questionnaire 2	n	%
1- What are the risk factors for developing breast cancer?		
Being a woman		
Yes	609	53.8
No	524	46.2
Being over 40 years old		
Yes	885	78.1
No	248	21.9
Woman who never got pregnant		
Yes	460	40.6
No	673	59.4
Cases of breast cancer in 1st degree relatives		
Yes	1,020	90.0
No	113	10.0
Alcohol use		
Yes	453	40.0
No	680	60.0
Menarche before age 12 and last menstruation after age 55		
Yes	220	19.4
No	913	80.6
Breast pain		
Yes	541	47.7
No	592	52.3
Breast cyst		
Yes	657	58.0
No	476	42.0
Obesity		
Yes	333	29.4
No	800	70.6
First child after 34 years old		
Yes	251	22.2
No	882	77.8
Smoking		
Yes	747	65.9
No	386	34.1
2- What are the complaints and/or changes that may suggest breast cancer?		
Spontaneous outflow of bloody nipple secretion		
Yes	791	69.8
No	342	30.2
Nodule		
Yes	1,081	95.4
No	52	4.6

Continue...

Table 2. Continuation.

Questionnaire 2	n	%
Skin retraction		
Yes	400	35.3
No	733	64.7
Bulging of the skin		
Yes	355	31.3
No	778	68.7
Nipple injury		
Yes	450	39.7
No	683	60.3
3- What breast cancer prevention measures do you consider most important?		
Monthly self-examination, annual clinical examination and annual breast resonance		
Yes	108	9.5
No	1,025	90.5
Monthly self-examination, annual clinical examination and annual mammography		
Yes	1,008	89.0
No	125	11.0
Monthly self-examination, annual clinical examination and annual ultrasound		
Yes	196	17.3
No	937	82.7
4- What strategies do you use to guide the users of your Health Unit?		
Individual consultation		
Yes	637	56.2
No	496	43.8
Educational group meetings		
Yes	586	51.7
No	547	48.3
Home care		
Yes	735	64.9
No	398	35.1
None		
Yes	8	0.7
No	1,125	99.3
Other		
Yes	82	7.2
No	1,051	92.8

or favor the continuing education of professionals, being limited to specific courses and training initiatives. These strategies contrast with the results of a study conducted in Petrópolis (RJ), where an initiative to train health professionals resulted in the improvement of several public health indicators[15].

Strategies like the one developed in Rio de Janeiro show the relevance of training PHC professionals for more effective actions. In this study, the verification of inappropriate concepts related to breast cancer risk factors, prevention and diagnosis among health professionals possibly translates into inadequate guidance for the population. However, only 33% of health professionals recognize that their knowledge about the subject needs improvement.

The identification of breast cancer etiological factors is important for the primary prevention of the disease[16]. In our study, the assessment showed satisfactory knowledge by health professional regarding some risk factors, such as age and family history[16]. On the other hand, breast tenderness and breast cysts were considered risk factors by about half of the professionals interviewed, which is an inadequate concept and can cause concern in the population. Furthermore, they can lead to unnecessary referrals and saturation of secondary and tertiary services, compromising resolvability[17].

Considering the modifiable risk factors, the number of professionals who do not associate obesity and alcohol consumption with increased risk for breast cancer stands out. Studies conducted in the city of Goiânia (GO), in agreement with the literature, identified that alcohol consumption[18] and the amount of abdominal fat increase the risk of breast cancer[19]. Therefore, it should be emphasized that the identification of these risk factors contributes to specific strategies for breast cancer primary prevention[16,19].

The diagnostic workup for breast cancer is multimodal and must be adapted to the different clinical presentations of the disease. In early stages, it is commonly asymptomatic and presentes no changes upon physical examination. Therefore, signs such as skin retraction, skin bulging and nipple injury are indicative of locally advanced disease and must be promptly recognized and properly managed[20]. In our study, only 30% of professionals identified these changes as suspected breast cancer, which could perpetuate a late diagnosis of the disease. Currently, in Brazil, these and other alterations in the self-examination and/or clinical examination of the breasts are responsible for about 50% of breast cancer diagnoses[21], reinforcing the importance of primary health professionals in the early diagnosis of the disease.

Barriers to accessing infrastructure are one of the daily adversities for secondary prevention. According to our findings, access to mammography was the main difficulty faced in the consolidation of preventive practices, both by users (71.5%) and health professionals (63.4%), a fact that goes against the number and the adequate distribution of mammography devices in the state, although there is low mammographic production[22-24]. In addition, the distribution of breast cancer professionals in the state is also disproportionate in relation to the population distribution, with 43 breast cancer specialists registered in Goiânia and only ten professionals registered in the countryside of the state[25,26], which explains the difficulty identified in accessing specialized services.

Table 3. Difficulties and challenges experienced by users and Primary-Care professionals in relation to the prevention and diagnosis of breast cancer (n = 1,099). Goiânia, Clinical Hospital, Universidade Federal de Goiás, 2020.

Questionnaire 3	n	%
Regional boards		
Estrada de Ferro (Catalão)	65	5.9
West I (Iporá)	181	16.5
West II (São Luís de Montes Belos)	152	13.8
Serra da Mesa (Uruaçu)	134	12.2
North (Porangatu)	79	7.2
North surroundings (Formosa)	128	11.6
Northeast II (Posse)	89	8.1
Southwest I (Rio Verde)	154	14.0
Southwest II (Jataí)	117	10.6
1 - What difficulties do you identify in carrying out breast cancer prevention actions in your municipality?		
Knowledge about the topic		
Yes	363	33.0
No	736	67.0
Support from local institution		
Yes	371	33.8
No	728	66.2
Lack of educational material		
Yes	598	54.4
No	501	45.6
Referral for a mammography service		
Yes	699	63.6
No	400	36.4
Referral for a specialized service		
Yes	611	55.6
No	488	44.4
Other		
Yes	92	8.4
No	1,007	91.6
2 - What facilities do you identify in breast cancer prevention actions?		
Knowledge about the topic		
Yes	611	55.6
No	488	44.4
Support from local institution		
Yes	418	38.0
No	681	62.0
Lack of educational material		
Yes	395	35.9
No	704	64.1
Referral for a mammography service		
Yes	400	36.4
No	699	63.6
Referral for a specialized service		
Yes	238	21.7
No	861	78.3
Other		
Yes	86	7.8
No	1,013	92.2
3 - What difficulties do the users of your service face for breast cancer prevention?		
Access to the women's annual consultation at the health unit		
Yes	185	16.8
No	914	83.2
Access to mammography		
Yes	786	71.5
No	313	28.5
Access to medical consultation in a specialized service		
Yes	705	64.1
No	394	35.9
Myths and taboos about breast cancer		
Yes	376	34.2
No	723	65.8
Difficulty in exposing the body for breast examination		
Yes	357	32.5
No	742	67.5
Other		
Yes	54	4.9
No	1.045	95.1
4 - What makes breast cancer prevention easier for users of your unit?		
Access to the women's annual consultation at the health unit		
Yes	743	67.6
No	356	32.4
Home care by the family health team		
Yes	646	58.8
No	453	41.2
Participation in educational group meeting		
Yes	508	46.2
No	591	53.8
Other		
Yes	72	6.6
No	1.027	93.4

Continue...

Another point to be highlighted is the perception of health professionals about the difficulties experienced by users in breast cancer prevention. In addition to factors related to the flow of assistance, around 30% of users are still susceptible to myths and taboos about the disease, as well as personal restrictions to expose their bodies to breast examinations. These data reinforce the need for educational actions aimed at the lay population, whose misinformation can restrict breast cancer screening and early diagnosis. In recent years, in response to this social demand, the Brazilian Society of Mastology has taken on a leading role creating various booklets and educational campaigns in various media[27].

The limitations found in this study are in line with what is proposed by the Brazilian model of basic health care, which was developed to articulate health promotion, as well as the reference to more complex services in indicated cases. However, even with 40 thousand teams and coverage of approximately 60% of the population, studies still point to problems in the quality of health care practiced in Brazil[28]. The training of health professionals appears, then, as a path to be followed to ensure better assistance to the population served by the Unified Health System[15]. Nevertheless, basic care also represents a privileged space for the development of permanent health education.

Together, the data presented in this study reinforce the need for investments in the structure of basic health care and in the team's continuing education, providing comprehensive care to the individual, health promotion and early diagnosis of breast changes. As a result, these measures could facilitate the diagnostic process of breast cancer and possibly improve the oncological outcomes of the disease.

CONCLUSION

The PHC professionals of the state of Goiás who participated in this project had, for the most part, completed high school and less than ten years of professional experience. They showed to have limitations regarding knowledge about primary and secondary prevention of breast cancer, as well as experience difficulties in care activities mainly related to access to mammography and to specialized services.

AUTHORS' CONTRIBUTION

R.M.S.R.: Conceptualization, Funding acquisition, Investigation, Methodology, Investigation, Project administration, Supervision, Validation, Visualization, Writing — revision & editing. D.C.N.R.: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing — original draft, Writing — revision & editing. R.S.C.: Data curation, Formal analysis, Investigation, Writing — revision & editing. L.R.S.: Investigation, Validation, Visualization, Writing — original draft, Writing — revision & editing. S.H.F.: Data curation, Formal analysis, Investigation, Writing — revision & editing. P.H.A.P.: Methodology, Validation, Writing — revision & editing. N.A.M.A.: Conceptualization, Data curation, Visualization, Writing — revision & editing.

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ORIGINAL ARTICLE
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Impact of the 21-Gene Recurrence Score (Oncotype DX®) on adjuvant therapy decision-making: a collaborative multicenter cohort study from Argentina

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ABSTRACT

Introduction: At present, more than half of patients diagnosed with early-stage breast cancer (BC) and express hormonal receptors will receive some adjuvant chemotherapy scheme, but only a few of them would benefit in terms of survival. Genomic platforms allow a better understanding of the heterogeneity of different types of hormonal receptor-positive and HER2-negative BC. They have proven their validity as tools to identify those patients who will obtain a clear benefit with the indication of chemotherapy treatment. The aim of this study is to analyze the use of the genomic platform, namely, Oncotype Dx® and its impact on the indication of adjuvant treatment, evaluated mainly as the change in treatment indication. **Methods:** Multicenter observational cohort study was performed in different Mastology units in Argentina. Patients underwent the Oncotype Dx to clarify the adjuvant treatment. Treatment decisions were settled before and after performing Oncotype Dx. **Results:** From January 2013 to December 2018, 211 patients with luminal A or B and HER2-negative breast carcinomas, who underwent the Oncotype Dx, were included. Based on our records, 40% of the patients change the indication of adjuvant treatment after the performance of the Oncotype Dx. Of these, 24% of patients who underwent initial endocrine therapy only adjusted their treatment with the addition of chemotherapy. Among patients with an initial CTH recommendation, 49% were able to receive endocrine therapy only when, due to traditional prognostic factors, they would have received chemotherapy. **Conclusions:** In our population, the use of the Recurrence Score was clinically significant in relation to the change of the established treatments. Consequently, it is a very important tool and a decisive factor in the adjuvant indication in patients with positive hormonal receptors and HER2neu-negative early BC.

KEYWORDS: breast neoplasms; genomics; chemotherapy, adjuvant; medication therapy management.

INTRODUCTION

Over the past years, genomic and molecular analysis has played a major role of significant relevance in the treatment of patients with breast cancer (BC). Approximately 60% of patients diagnosed with early-stage hormone receptor-positive BC will be offered adjuvant treatment that includes chemotherapy, though only 2–10% of patients will receive the benefit in terms of survival[1,2]. The development and the use of gene expression assays have provided us with an in-depth understanding of the remarkable heterogeneity of the different types of BC[3]. These tests have proven their validity as tools that allow the identification of patients who are most likely to gain survival advantage from adjuvant chemotherapy[4]. Subsequently, this responds to two specific premises in the treatment of BC: tailoring of adjuvant systemic therapy and adjusting it according to each patient's specific risk for BC recurrence, which subsequently results in decreased exposure of patients to undesirable toxicity and potential side effects associated with chemotherapy[4-6].

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Based on the assessment of 21 tumor genes, Oncotype DX® is one of the most widespread and globally available gene expression assays. This diagnostic test results in a numerical prognostic index named Recurrence Score (RS) that ranges from 0 to 100, and it is the result of a mathematical algorithm, which correlates with the predicted risk of distant metastasis over the following 10 years. Traditionally, BC prognosis and, consequently, subsequent systemic adjuvant therapy were established through clinical and pathological parameters. The use of genomic assays, such as Oncotype DX, has been associated with a significant impact on clinical decision-making regarding the indication of adjuvant therapy, ranging between 27% and 74% according to different series[7,8].

The prospective randomized TAILORx study proved that most patients with early-stage hormonal receptor-positive and HER2neu-negative BC do not benefit from adjuvant chemotherapy and established Oncotype DX as a standard of care[9]. Regarding treatment decision-making in patients with node-positive BC, the results of the prospective trials are still awaiting publication. These trials will also probably validate the use of RS as a clinical tool for chemotherapy de-escalation in this subset of patients. Nonetheless, based on the available retrospective evidence, several workgroups have already begun to incorporate RS in the management of up to 51% of patients with axillary metastasis (1–3 positive nodes). In this subset of patients, the impact on treatment decisions is large, given that it frequently allows the avoidance of unnecessary and potentially toxic chemotherapy[10,11].

OBJECTIVES

The primary goal of this study was to explore the use of Oncotype DX RS and its impact on adjuvant treatment decision-making through the assessment of change in the indication of chemotherapy. The secondary goal was to describe the clinical and pathological characteristics of the study population and the adjuvant treatments offered to the included patients.

This study was carried out due to the collaborative efforts from some of the main breast units of Argentina. A novel cooperative initiative has not been previously performed throughout our country.

MATERIALS AND METHODS

This study is a multicentric observational cohort study. It was carried out in the breast units of the following hospitals and clinics of Argentina: Hospital Italiano (Buenos Aires), Hospital Universitario Austral, Hospital Italiano (La Plata), Hospital Británico, Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno," Instituto Alexander Fleming, and Centro de Mastología de Rosario.

The study period was from January 2013 to December 2018. The inclusion criteria were patients diagnosed with luminal A or B and HER2-negative invasive BC who were diagnosed, treated, and followed at different participating breast units and who received Oncotype DX testing. Clinical and pathological data were obtained from a review of medical records at each center. All patients and adjuvant treatment decisions were discussed and documented during the weekly Tumor Boards at each corresponding center.

With regard to pathology analysis, hormone receptor status was assessed by automatized immunohistochemistry and quantification using Allred Score (intensity + proportion). HER2neu status was also examined using automatized immunohistochemistry and, in the case of equivocal results (2+), was confirmed using molecular biology techniques, according to availability at each center: fluorescent *in situ* hybridization, chromogenic *in situ* hybridization, or silver *in situ* hybridization. Luminal A and B tumors were stratified according to Ki67, which was assessed by calculating the average of three fields.

In all cases, adjuvant treatment was discussed and documented before performing Oncotype DX, based on the clinical and pathological characteristics of each patient and tumor. The pretest decision was registered on the treatment registry at each site. After posttest RS was available, the committee re-evaluated each scenario and redefined the proposed treatment plan. This adjuvant schema was also documented in the registry log, allowing the assessment of modifications in treatment decision-making. All patients were offered and agreed to undergo the posttest treatment plan. In patients with intermediate RS scores, adjuvant treatment was recommended based on traditional predictive and prognostic markers, while considering patient preference as well.

Statistical analysis

Continuous variables are presented using average (mean) and standard deviation. Quantitative variables are expressed as medians and interquartile ranges. Categorical variables are described by observed and relative frequency (percentage). Estimated probabilities below 5% were considered statistically significant. Statistical analysis was performed using PSPP 0.8 software.

Ethical considerations

Given the implications of this study, all the investigators involved in its development were familiar with the ethical, legal, and judicial requirements for clinical research, as established by National and International standards such as the Declaration of Helsinki. Since the information was obtained through detailed analysis of the medical records of the patients treated at different sites and that the result of this study under no circumstance has direct effects on the included patients, the need for informed consent was disregarded. To assure the maximum confidentiality and anonymity of patient data, each site entered data into a coded

database which was accessed only by the authorized investigators (Dr. Allemand and Dr. Valerio), according to the National Law of Protection of Personal Data 25.326 (*habeas data*).

RESULTS

Between January 2012 and December 2018, 211 patients with luminal A or B and HER2-negative invasive BC who underwent assessment with Oncotype DX were included. All the patients were diagnosed, treated, and followed up at one of the participating breast units. The clinical and pathological characteristics of these patients are given in Table 1. Most patients were at stage 1 (72%) ductal carcinomas (76%). Only 24 patients (11%) had positive lymph nodes.

The distribution of Oncotype DX RS in the study population (n=211) resulted as follows: 42 patients (20%) had a low-risk RS, 107 patients had an intermediate-risk RS (51%), and 62 patients had a high-risk RS (29%). If we consider the RS of those assays that were ordered before the modification of the cutoff points published in the TAILORx study (n=176), the distribution differed moderately: 92 patients (52%) had low-risk scores, 53 patients (30%) had intermediate scores, and only 31 patients (17%) had high-risk scores (Table 2).

Adjuvant endocrine therapy, alone or in combination with chemotherapy, was prescribed according to standardized international guidelines and consensus as well as site-specific clinical practice guidelines. To analyze the results, we considered the date at which Oncotype DX was performed, given that a significant number of patients were treated before TAILORx was published. Among 176 patients who were treated before the publication of this study, adjuvant treatment was distributed as follows: all patients with low-risk RS received endocrine therapy alone, and all patients with high-risk RS received chemotherapy and subsequent endocrine therapy, according to international standards. For patients with intermediate RS and for patients with RS greater than 24, chemotherapy was offered based on traditional prognostic factors (i.e., axillary status, size, grade, and lymphovascular invasion)[4].

Table 2. Recurrence score.

Pre Tailor Recruited Patients		Patients N=211	%
Low Risk	0-17	92	52
Intermediate risk	18-30	53	30
High risk	31-100	31	18
Pos Tailor Recruited Patients			
Low Risk	0-10	8	20
Intermediate risk	11-25	16	51
High risk	26-100	11	29

Table 1. Clinicopathological characteristics and recurrence score.

Clinicopathological characteristics	N (%)	RS<11	11 . 25	>25	
Stage					
I	148 (72)	27 (12.7)	83 (39.3)	38 (18)	p=0.16
II	62 (29.3)	5 (2.3)	34 (16.1)	23 (10)	
III	1 (0.5)	0	0	1 (0.5)	
Histological Type					
Ductal invasive carcinoma	162 (76.7)	18 (11.1)	88 (54.3)	56 (34.6)	p=0.009
Lobular	30 (14.2)	6 (20)	20 (66.7)	4 (13.3)	
mucinous	3 (1.4)	2 (66.7)	1 (33.3)	0	
others	16 (7.5)	6 (2.8)	8 (3.7)	2 (0.9)	
Estrogen receptor					
Negative	1 (0.5)	0	0	1	p=0.299
Positive	210 (99.5)	32 (15.2)	117 (55.8)	61 (29)	
Progesterone receptor					
Negative	21 (9.9)	0 (0)	6 (28.5)	15 (7.5)	p=0.0001
Positive	190 (90.09)	32 (16.9)	111 (58.4)	47 (24.7)	
Nodal involvement					
Negative	178 (84.3)	20 (15.5)	100 (53.5)	58 (31)	p=0.45
Isolated tumor cells -micrometastases	9 (4.2)	2 (22.2)	6 (66.7)	1 (11.1)	
Macrometástasis	12 (5.6)	0	9 (75)	3 (25)	
Capsular perforation	4 (1.8)	1 (33.3)	3 (66.7)	0	

Thirty-five patients were included after TAILORx was published. Treatment offered in the high- and low-risk RS groups was similar to that of the previously described subset of patients. However, for patients with intermediate scores, age was factored into the treatment plan: patients who aged >50 years received endocrine therapy alone, and patients who aged <50 years were offered chemotherapy if the RS was greater than 21 and based on traditional prognostic factors.

Considering the information collected from the tumor board registry logs, we found that in 84 patients (40%), Oncotype DX was decisive in changing the initial treatment plan. Nineteen patients who had initially not been considered for chemotherapy were finally offered cytotoxic therapy (23%). The remaining 77% of patients who changed the initial treatment were considered eligible for chemotherapy based on traditional prognostic factors but ended up receiving endocrine therapy after RS was performed. Before RS, 63% of patients were considered for chemotherapy, and 37% of patients were considered for endocrine therapy (Figure 1). After RS was performed, most of them could receive only endocrine therapy (59%). When describing the relative impact of the change in treatment indication (percentage) and the distribution according to definitive treatment, 60% of patients were considered at initial indication, and 40% were not.

When analyzing adjuvant treatment as a whole, 85 of 211 patients (40%) received adjuvant treatment with both chemotherapy and endocrine therapy. Among these, 24 patients underwent chemotherapy with six cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Thirty-three patients received combined anthracycline and taxane-based chemotherapy (4 cycles of adriamycin and cyclophosphamide + 12 cycles of weekly paclitaxel). Seven patients underwent 4 cycles of AC, and the remaining 23 patients received other chemotherapy regimens. As for endocrine therapy, 50 patients received tamoxifen, 23 patients received anastrozole, and 8 patients received a combination of tamoxifen or anastrozole plus ovarian suppression with luteinizing hormone-releasing hormone (LHRH) agonists (Goserelin). Notably, 130 patients received endocrine therapy exclusively. Among these, 78 patients received tamoxifen, 43 patients received aromatase inhibitors, and 9 patients received some form of endocrine therapy in addition to LHRH agonists (Goserelin).

We also included 24 patients with positive lymph nodes. Of note, 9 patients had sentinel lymph node micrometastases, and 15 had macrometastases. Two patients underwent axillary lymphadenectomy without the presence of other positive nodes. Of these 15 patients, 4 patients underwent anthracycline-based chemotherapy, and 11 patients received endocrine therapy based on their RS.

We performed a subanalysis considering the result of the RS and its correlation with different clinical and pathological factors such as patient age, size, tumor grade, and Ki67 status (Figures 2-5). When analyzing age, 25% of women who were below 40 years had a high-risk RS (>25), 54% had an intermediate-risk RS (11–25), and 21% had a low-risk RS. In addition, 26% of women who were above 70 years had a high-risk RS. Considering tumor size, 24% of patients with tumors up to 2 cm presented a high-risk RS, while patients with larger tumors had more high-risk RS (50%; p=0.001). When analyzing histological grade, only two patients with low-grade tumors had a high-risk RS; and 50% of high-grade tumors had low (8%) and intermediate (43%) RS (p=0.0001). Considering Ki67, we can observe a certain correlation

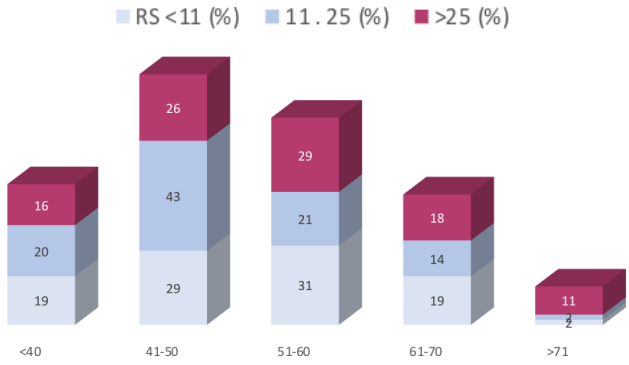

Figure 2. Age and recurrence score.

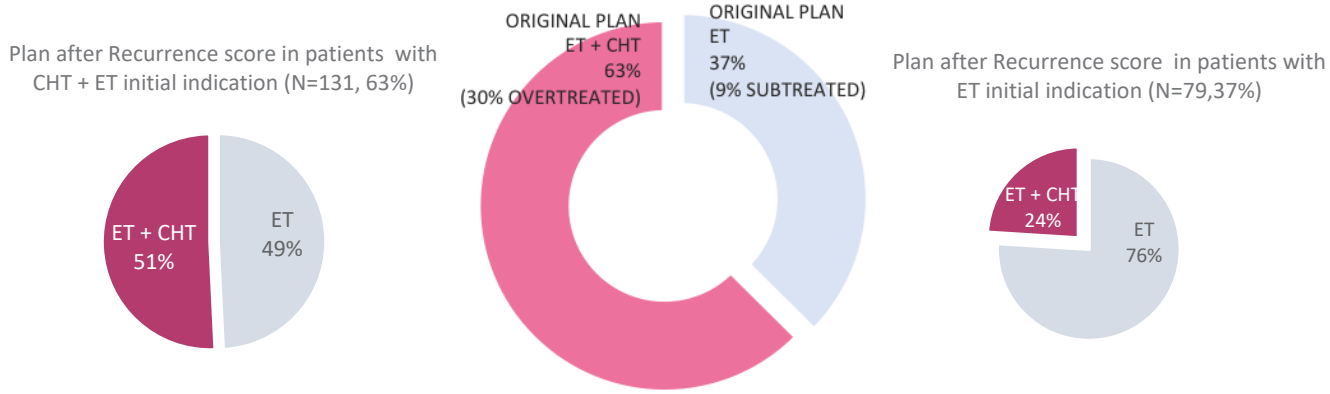

Figure 1. Treatment indication before and after recurrence score (N=211).

between this value and the RS. However, it is not absolute as 16% of patients with Ki-67 <14% had a high-risk RS (RS>25), and 12% of the patients with Ki-67 >30% had a low-risk RS. These results are similar to those published in the literature. Gluz in Plan B already showed this correlation and mentioned that approximately 15% of patients with Ki-67 <20 presented a high-risk RS (RS>25), and also a non-negligible percentage of patients with Ki-67 >30 had a low-risk RS[12].

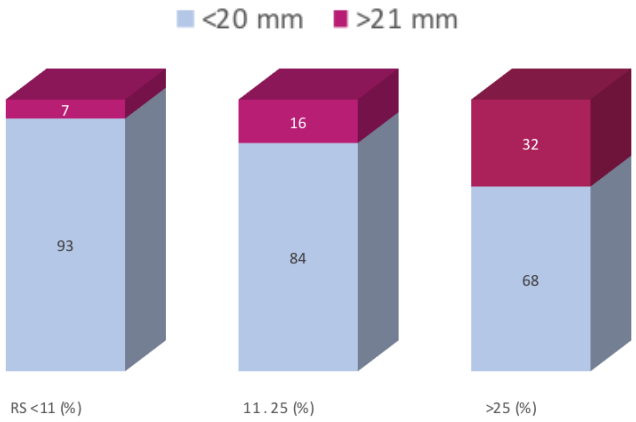

Figure 3. Size and recurrence score.

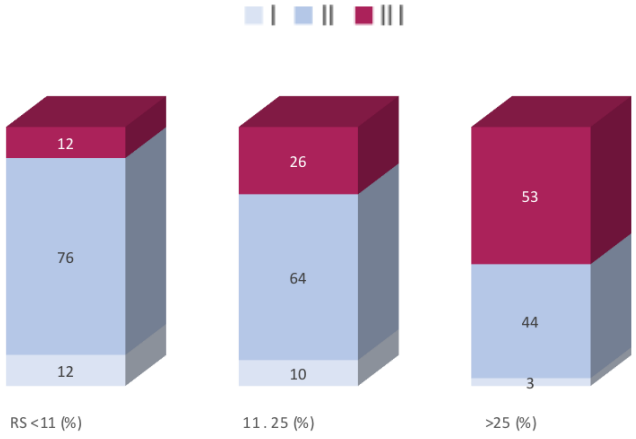

Figure 4. Tumor grade and recurrence score.

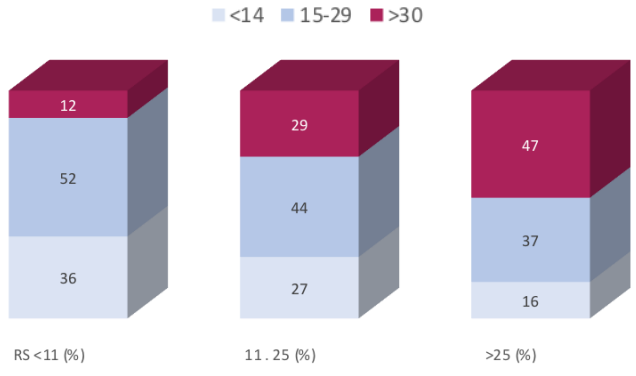

Figure 5. Ki 67 and recurrence score.

DISCUSSION

Adjuvant systemic treatment has significantly increased disease-specific survival for patients with BC. Nonetheless, even when optimum treatment is readily available, many patients do not receive the treatment that best fits their specific needs. This frequently leads to overtreatment (the indication of cytotoxic drugs from which benefit will not be derived) and undertreatment. This underscores the importance of developing biomarkers that may offer a chance to correctly stratify patients according to their risk of recurrence, thus allowing greater precision in therapeutic decision-making[6,13].

Until the past decade, adjuvant treatment recommendations were based primarily on traditional, clinical, anatomical, and pathological factors as well as immunohistochemistry. Aside from the role of the estrogen receptor as a predictive factor for endocrine therapy response or the expression of *her2neu* and its prediction of response to monoclonal antibody therapy, up to now, there has been scarce evidence of any specific biomarker that could predict benefit from chemotherapy.

The development of Oncotype DX and, consequently, the RS® has provided a valuable tool for the correct stratification of patients based on their specific risk for distant metastasis. The RS has been studied both prospectively and retrospectively. The retrospective validation studies were designed based on the long-term follow-up of the NSABP B-14 and NSABP B-20 trials, which evaluated and surveilled the patients treated with upfront tamoxifen versus tamoxifen plus chemotherapy with CMF[7,8,14].

In the published literature, a variable impact of using the RS has been described in the indication of adjuvant systemic treatment. This variability is evidenced in therapeutic changes from its use, which ranges between 27% and 74% depending on the series that are taken into consideration, the adjuvant treatment guidelines most commonly consulted in each population, and also the availability to perform the genomic study[10,11,15]. Publication of prospective validation studies in patients with positive axilla is still awaited in order to extend the utility spectrum of RS. However, based on retrospective validation studies, several groups have already published reports showing a therapeutic change in 51% of patients with positive nodes (1–3 lymph nodes); according to RS, up to 33% of patients with a positive lymph node have not shown the indication of potentially non-beneficial chemotherapy[16,17].

The TAILORx study, published in 2018[9], showed that most patients with early-stage hormone receptor-positive BC do not benefit from the combination of chemotherapy and endocrine therapy. This prospective validation study positioned the Oncotype DX RS as a standard of care in the management of early-stage luminal, *her2*-negative BC, which currently allows a more tailored approach to adjuvant therapy planning. TAILORx reported that up to 73% of patients who were considered at high risk based on traditional features

obtained an RS between 0 and 25 and were thus likely to have been overtreated if adjuvant therapy had been indicated based only on clinical variables. In contrast, 43% of patients with RS ranging between 26 and 100 had previously been considered at low clinical risk and would probably have received inadequate treatment. It has been proposed that RS could allow the identification of up to 85% of women who could be spared adjuvant chemotherapy, especially in the postmenopausal subgroup with RS who aged below 25 and in patients who aged below 50 years, with an RS of £15. In our series, 44% of the patients with RS >26 were considered at low clinical risk based on traditional features, similar to what Sparano reported, while 16% of patients with RS <10 were considered at high clinical risk (Figure 6).

As we mentioned earlier, the distribution of Oncotype DX results based on the current RS classification was as follows: 20% received a low RS, 51% received an intermediate RS, and 29% received a high RS similar to what was published in the TAILORx study: 27%, 43%, and 30%, respectively[9].

In our series, we have described a change in adjuvant therapy decision in approximately 40% of patients, with a significant reduction in the use of chemotherapy. When analyzing the original treatment plan, 79 patients (37%) received endocrine therapy exclusively according to clinicopathological features, while 131 patients (63%) received chemotherapy combined with endocrine therapy. After RS was performed, we could notice changes in treatment recommendations: 25% of patients who underwent initial endocrine therapy only finally added chemotherapy treatment, and in patients with an initial CTH recommendation, 49% were able to receive endocrine therapy only. In other words, one-fourth of patients in the initial endocrine therapy only treatment would have been undertreated, and almost half of patients in the initial CTH recommendation would have been overtreated according to the genomic platform (Figure 1).

This proportion correlates with the published literature, although it tends toward the higher end. We believe that this may be attributed to a selection bias. As shown in Table 1, most of the patients included were patients with luminal B-like tumors, stratified according to Ki67. This is related to the fact that in our country, Oncotype DX is not covered by most health insurance providers for patients clinically at low risk but is usually covered when Ki67 is above a specific cutoff point. This means that patients often need to finance the assay on their own, and many do not have the means to do so. This distribution probably explains why the proportion of decision change is at the higher end of the range.

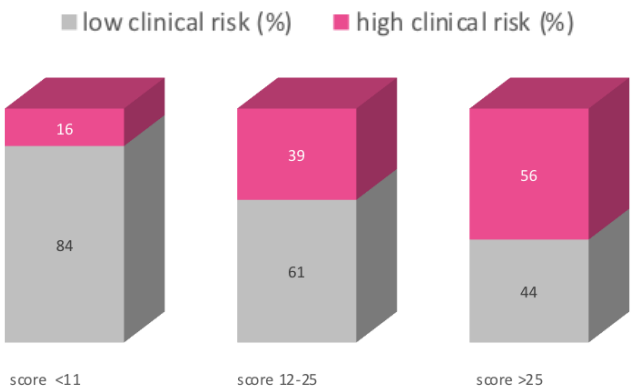

Figure 6. Clinical risk and recurrence score.

Currently, due to the advancement in adjuvant endocrine therapy, events during follow-up (local and distant recurrences) are significantly reduced. We acknowledge that a longer follow-up time is warranted in order to increase the power to long-term events and to assess survival.

CONCLUSIONS

In our study population, the use of the genomic platform Oncotype DX and the RS resulted clinically significant in terms of the change in prescription of adjuvant therapy, thus constituting a decisive factor for treatment decision in patients with early-stage hormonal receptor-positive and HER2neu negative BC. Although availability is still a limiting factor in developing countries such as Argentina, we find that RS is a desirable and valuable marker that will allow treatment tailoring and avoidance of exposure to undesirable side effects as well as not withholding adjuvant chemotherapy from those who are most likely to obtain a benefit in terms of survival.

Impact of Recurrence Score (RS) on adjuvant therapy decision-making is a multicenter observational cohort study performed in different Mastology units in Argentina. In our country, this is a novel cooperative initiative that joined us with the aim of analyzing the use of the RS and its impact on the treatments, evaluated mainly as a change in indication.

AUTHORS' CONTRIBUTIONS

C.A.: conceptualization, formal analysis, writing — original draft, writing — review and editing, project administration, resources, software, and supervision.
A.C.V.: conceptualization, formal analysis, writing — original draft, writing — review and editing, project administration, resources, and software.
M.F.C.: writing — original draft, and writing — review and editing.
G.I.: formal analysis, and methodology.
I.M.: conceptualization, data curation, and resources.
F.T.: conceptualization, data curation, and resources.
J.L.U.: conceptualization, data curation, and resources.
F.C.: conceptualization, data curation, and resources.
F.V.S.: conceptualization, data curation, and resources.
L.B.G.: conceptualization, data curation, and resources.

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ORIGINAL ARTICLE
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Prognostic role of 18F-FDG PET-CT in the prone position in the evaluation of invasive breast carcinoma

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ABSTRACT

Introduction: The objective of this study was to correlate the features of invasive breast carcinoma in 18F-FDG positron emission tomography/computed tomography with histopathological results, findings from other imaging methods, and survival. **Methods:** This observational single-center study included patients who underwent staging 18F-FDG positron emission tomography/computed tomography between September 2012 and April 2019; the results were correlated with the findings of other imaging tests and anatomopathological results. Lesions were evaluated for their maximum standardized uptake value on positron emission tomography/computed tomography performed in the prone position. Tumors were classified into three subtypes (luminal, HER2 and triple-negative) based on immunohistochemical analyses. **Results:** A total of 125 patients with a mean age of 52 years (24–90 years) were analyzed. The primary tumor showed an increased 18F-FDG concentration on positron emission tomography/computed tomography in 122 (97.6%) patients, with a mean maximum standardized uptake value of 7.15 (1.0–32.9 range). The mean maximum standardized uptake value was higher in the triple-negative subtype (11.4; n=24) than in the luminal (6.2; n=89) and HER2 (5.0; n=9) subtypes (p<0.01). Tumors with more aggressive histological and immunohistochemical characteristics showed higher maximum standardized uptake values. Patients with a standardized uptake value greater than 7 in the primary tumor or greater than 6.7 in the axillary lymph nodes had poor overall survival (p=0.03 and p<0.01, respectively). **Conclusions:** Our study suggests that the maximum standardized uptake value obtained on positron emission tomography/computed tomography in the prone position may correlate with the tumor immunophenotype and overall survival regardless of the treatments performed, and can be used as a prognostic biomarker in invasive breast carcinoma patients.

KEYWORDS: breast neoplasms; PET/CT; triple negative breast cancer; survival.

INTRODUCTION

Breast cancer is the most common malignancy in the female population and is the leading cause of cancer-related death in these patients[1]. Breast imaging methods such as mammography, ultrasound and magnetic resonance imaging (MRI) have a fundamental role in diagnosis and locoregional treatment planning[2-4].

Positron emission tomography/computed tomography (PET-CT) with 18F-fluor-deoxi-glucose (18F-FDG) can provide information related to glucose metabolism in different organs and tissues. For patients with breast cancer, this test is generally used to detect distant metastases and recurrences, and evaluate therapeutic responses. However, prior studies have shown that PET-CT can also be used to assess breast tumors. Prone PET-CT with a dedicated protocol for breast evaluation improves the ability to detect and characterize breast cancer, allowing better correlation with conventional breast imaging methods[5-9]. The tumor maximum standardized uptake value (SUVmax) obtained from 18F-FDG PET-CT performed with a specific breast protocol correlates better with tumor aggressiveness and can be used as a prognostic biomarker in patients with invasive breast carcinoma.

The objective of this study was to correlate the features of invasive breast carcinomas in prone 18F-FDG PET-CT scans using a dedicated breast protocol with radiological findings from conventional breast imaging methods (mammography, ultrasound and MRI), as well as histopathological results and overall survival.

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METHODS

This observational, retrospective and single-center study was approved by the institutional review board, and informed consent was waived. We included female patients who had histology-proven invasive breast carcinoma and underwent staging 18F-FDG PET/CT between September 2012 and April 2019, with a dedicated protocol for breast evaluation. From 979 PET/CT exams performed in breast cancer patients during the study period, 631 were excluded because patients did not undergo treatment/follow-up at the institution or had incomplete histological or immunohistochemistry analysis. Additionally, 223 patients were excluded because they underwent some treatment before the PET/CT exam (131 had neoadjuvant chemotherapy and 92 had prior surgical resection), and 125 patients were included in the final analysis.

Pathological analysis

The histopathological diagnosis was performed through analysis of the surgical specimen in 93 patients and percutaneous biopsy in the remaining cases. All biopsies were reviewed by the institution's Department of Pathology. The following histological features were assessed: histological type, presence of an associated *in situ* carcinoma, histological grade, nuclear grade, mitotic index, associated aspects of necrosis, desmoplastic reaction, inflammatory infiltrate, and vascular, perineural and lymphatic invasion.

Breast carcinomas were classified into 3 subtypes based on immunohistochemical expression of hormone receptors and HER2: luminal, positive hormone receptors; HER2-overexpressing, negative hormone receptors and positive HER2; and triple-negative, negative hormone receptors and HER2. Estrogen receptor (ER) and progesterone receptor (PR) were considered positive when => 1% in neoplastic cells, and HER2 was considered positive or overexpressed if immunohistochemistry was 3+ or 2+ with positive gene expression on *in situ* hybridization (ISH)[10,11].

Imaging analysis

Whole-body PET-CT was performed on a dedicated device (PET-CT Gemini TF, Philips) 60–120 minutes after the intravenous administration of 0.154 mCi/kg of weight 18F-FDG in the supine position with capillary blood glucose concentrations below 150 mg/dL. Subsequently, an additional series of images was acquired dedicated for the breast evaluation, with the patient in prone position using an especially made device, which reproduces the coil used in breast MRI. The exam was performed on cephalocaudal acquisition with 2.5 mm-thick contiguous tomographic slices with no use of intravenous or oral contrast agent, followed by the acquisition PET images with 90 seconds acquisition time for each 15 cm bed position. The interpretation of the 18F-FDG PET/CT images was performed by at least two experienced nuclear medicine physicians who considered any areas of increased 18F-FDG uptake in relation to normal breast parenchyma to be positive. SUVmax was calculated in the images acquired in the prone position for each region of interest.

Mammography examinations were performed on a digital device in cranio-caudal and lateral oblique views, with compression between 11 and 18 kg/cm^3 (average 14 kg/cm^3), and with complementary views, if necessary. Ultrasound examinations were performed with a high-frequency transducer from 10–14 mHz, allowing evaluation of the breasts, axillary regions, internal mammary chain and infraclavicular region. MR images were acquired with the patient in the prone position on a 1.5 Tesla device (MAGNETOM Symphony, Siemens; Signa HDxt, GE; or Ingenia, Philips) using a dedicated breast coil before and after injection of the intravenous paramagnetic contrast medium (gadolinium), including T1- and T2-weighted images, dynamic contrast enhancement (DCE) and diffusion-weighted images. According to the BIRADS lexico, mammographic findings were categorized as calcification, asymmetry, architectural distortion or mass[12]. Ultrasound findings were classified as mass or non-mass lesions, and MRI findings were described as mass or non-mass enhancement.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 20.0. Variables are presented using absolute and relative frequencies (qualitative variables) or main summary measures (quantitative variables), such as the mean, standard, median, minimum and maximum deviation. Statistical tests were used, when necessary, to identify correlations between variables. The χ^2 test and Fisher's exact test were used to compare categorical variables; Student's *t* test (or the non-parametric Mann-Whitney test, as indicated) was used to compare quantitative variables between two groups. Kaplan-Meier curves were used to analyze overall survival. To compare the survival curves between different groups, the log-rank test and Cox regression were used to estimate the hazard ratio (HR) with a 95% confidence interval (CI). The level of significance adopted was 5% ($p \leq 0.05$).

RESULTS

This study analyzed 125 patients with a mean age of 52 years (range: 24-90 years), with 38.4% of the patients aged 50 years old or younger at the time of diagnosis. 18F-FDG PET-CT in the prone position was positive in 122 patients (97.6%), with a mean SUVmax of 7.15 (range: 1.00-32.90). Eighty-three patients (66,4%) had multifocal and/or multicentric disease, and 73 patients (58.4%) had suspected axillary lymph nodes on PET-CT, with a mean SUVmax of 5.37 (range: 1.30–26.30). 18F-FDG PET/CT in the prone position had a false-negative result in 3 patients who had luminal subtype; two had a breast MRI examination (one with mass and the other with non-mass enhancement), and one underwent mammography

and ultrasound examinations, both of which revealed only an area of architectural distortion.

Sixty-four (51.2%) patients underwent mammography, 81 (64.8%) patients underwent an ultrasound examination, and 101 (80.8%) patients underwent breast MRI (Table 1). There was no statistically significant difference in the SUVmax in relation to the mammography findings (p=0.527). On breast ultrasound and MRI, tumors that presented as a mass showed higher SUVmax values than non-mass lesions (p<0.001 for ultrasound and MRI).

There was a statistically significant correlation between the SUVmax and histological grade, nuclear grade, presence of inflammatory infiltrate, and subtype (Table 2). Tumors with the triple-negative subtype showed a higher SUVmax than those with the luminal and HER2 subtypes.

The mean follow-up period was 82.5 months; 13 patients had distant metastasis, 6 had locoregional recurrence, and 5 died in this period. Patients with an SUVmax in the primary tumor above 7 had worse overall survival than patients with an SUVmax equal to or less than 7 (71.4 x 85.8 months; p=0.030) (Figure 1). Regarding the SUVmax values of the axillary lymph nodes, patients with values above 6.7 had worse overall survival than patients with values less than 6.7 (p<0.001) (Figure 2). There was no correlation between the SUVmax and recurrence pattern.

Table 3 shows the results of Cox regression for overall survival in relation to age, subtype (triple-negative was only compared with Luminal due to the small number of HER2+ patients), SUVmax of the primary tumor, presence of an axillary lymph node with abnormal 18F-FDG uptake, and SUVmax of the axillary lymph nodes. Only the axillary lymph node SUVmax showed a significant correlation with overall survival, with the risk being 15.7% higher for each one-unit increase in the SUV.

Table 1. Findings Described in Conventional Imaging Tests and the Mean maximum standardized uptake values.

Findings	N (%)	Average SUVmax value	p
Mammography (n=64)			
Calcification	9 (7.2)	6.0	0.527
Asymmetry	12 (18.7)	8.0	
Architectural distortion	21 (16.8)	6.4	
Mass	29 (23.2)	6.4	
Ultrasound (n = 81)			
Mass	67 (53.6)	8.8	<0.001
Non-mass lesions	19 (15.2)	5.2	
Breast MRI (n=101)			
Mass	71 (67.3)	8.1	<0.001
Non-mass enhancement	30 (29.7)	4.7	

SUVmax: maximum standardized uptake value.

DISCUSSION

The results of the present study are in agreement with those in the literature, with an accuracy of 97.6% for detecting invasive breast carcinoma, whose lesions had SUVmax values ranging from 1.00–32.90. There is no consensus in the literature on the ideal cutoff SUVmax for the characterization of benign or malignant breast

Table 2. Histological and Immunohistochemical Characteristics of the Lesions and the Mean maximum standardized uptake values.

Features	N (%)	Average value SUVmax (median)	p
Histological grade			
I	12 (9.6)	3.7 (3.2)	0.011
II	39 (31.2)	5.8 (4.5)	
III	41 (32.8)	8.3 (6.8)	
Nuclear grade			
Low	5 (4.0)	3.6 (3.1)	0.016
Intermediate	22 (17.6)	4.5 (4.1)	
High	65 (52.0)	7.6 (6.1)	
Desmoplastic reaction			
Absent	4 (3.2)	9.3 (5.7)	0.224
Discreet	27 (21.6)	7.5 (4.5)	
Moderate	51 (40.8)	6.5 (5.2)	
Accentuated	9 (7.2)	3.6 (3.6)	
Inflammatory infiltrate			
Absent	3 (2.4)	4.6 (4.7)	0.046
Discreet	64 (51.2)	5.3 (4.1)	
Moderate	17 (13.6)	9.3 (6.2)	
Accentuated	7 (5.6)	13.3 (14.3)	
Vascular invasion			
Yes	2 (1.6)	6.7 (7.6)	0.651
No	89 (97.8)	6.7 (5.0)	
Perineural invasion			
Yes	4 (3.2)	3.3 (3.6)	0.199
No	87 (95.6)	6.8 (5.0)	
Lymphatic invasion			
Yes	13 (10.4)	6.1 (5.3)	0.738
No	78 (85.7)	6.1 (5.3)	
Subtype			
Luminal	92 (73.6)	6.2 (4.6)	<0.001
Triple Negative	24 (19.2)	11.4 (9.4)	
Her-2	9 (7.2)	5.0 (4.5)	
Associated DCIS			
Yes	41 (45.0)	6.0 (4.1)	0.228
No	50 (54.5)	7.3 (5.4)	

SUVmax: maximum standardized uptake value.

lesions. In the study by Chae[13] that evaluated 60 breast lesions, 32 of which were malignant and 28 benign, it was concluded that, at a cut-off value of 2.3, the rate of malignancy and specificity of the mean SUVmax for differentiating benign and malignant breast lesions were 61.3% and 76.3%, respectively[13]. Another study that evaluated 172 patients who underwent 18F-FDG PET-CT and breast MRI, both in the prone position, also demonstrated that the SUVmax value was not useful in differentiating benign from malignant lesions[7].

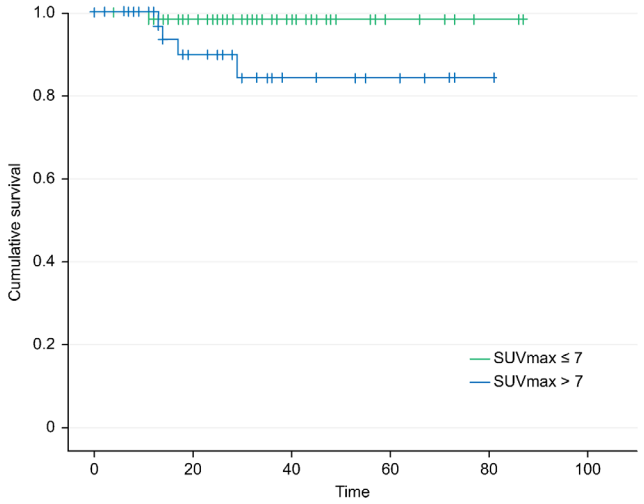

Figure 1. Overall survival of patients evaluated according to the maximum standardized uptake value in the primary tumor.

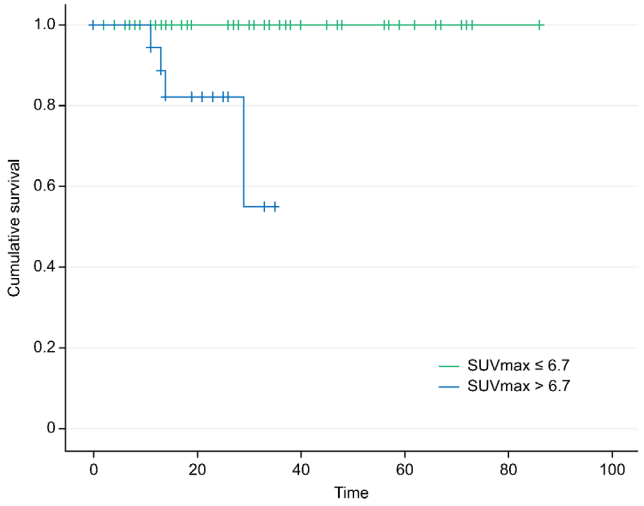

Figure 2. Overall Survival of Patients Assessed according to the maximum standardized uptake value of the Axillary Lymph Nodes.

Table 3. Cox Regression Values for Overall Survival.

Variables	HR	95%CI	p
Age	1.010	0.944–1.082	0.767
Immunophenotype NT	1.184	0.132–10.604	0.880
Primary tumor SUVmax	1.078	0.970–1.197	0.162
Presence of axillary lymph node in the Pet	3.098	0.346–27.735	0.312
SUVmax axillary lymph nodes	1.157	1.046–1.280	0.005

SUVmax: maximum standardized uptake value.

Our study showed that tumors with more aggressive histological and immunohistochemical characteristics, such as a high nuclear grade, histological grade III and the triple negative subtype, have higher SUVmax values. The same result was demonstrated in a study by Orsaria[14] that analyzed 50 patients with locally advanced or recurrent breast cancer. These patients underwent 18F-FDG PET-CT for preoperative staging, where it was observed that the average SUV was significantly different between tumor grades 1 (3.3±1.8), 2 (4.5±2.9) and 3 (5.8±3.3) (p=0.05). The authors also concluded that hormone receptor negativity, a high Ki-67 index and the triple-negative subtype were associated with increased 18F-FDG uptake[14]. However, this study was not performed with a dedicated coil for breasts in the prone position. Other reports in the literature have also demonstrated that the triple-negative molecular subtype has a high SUVmax that is proportional to its aggressive biological characteristics, with high sensitivity in FDG PET/CT images[15,16].

Regarding the limitations of this method, Avril[17] analyzed 144 patients with suspicious breast images who underwent FDG PET/CT, and concluded that the method has a high positive predictive value (96.6%) for breast cancer. However, the effects of partial volume and metabolic activity, which depend on the tumor type, are the most significant limitations of the examination[17]. The combination of PET/CT with other imaging methods, such as breast MRI, is promising and may lead to a reduction in the number of unnecessary biopsies[18,19].

The overall survival assessment in this study shows that patients with an SUVmax greater than 7 in the primary tumor and 6.7 in the axillary lymph nodes had poor overall survival. Several authors have investigated the usefulness of 18F-FDG PET/CT in predicting the clinical outcomes of patients with breast cancer, and have proposed cutoff values for the SUVmax. Jo[20] indicated that an SUVmax of 5.95 was the ideal cutoff value for predicting disease-free survival, whereas Ueda[16] indicated that an SUV of 4.0 may be one of the best values for predicting disease prognosis, with a significantly high incidence of mortality after 10 years in patients with an SUV above that cutoff[16]. In the present study, according to the multivariate analysis, only the SUVmax in the axillary lymph nodes showed a statistically significant correlation with overall survival.

The results of this work must be considered in the context of some limitations. This study was retrospective, and the final number of samples analyzed was small because many patients had insufficient data. FDG PET/CT results were included in this study regardless of the size of the lesion, and small tumors might have been underestimated due to the effect of partial volume. For multifocal and multicentric tumors, we only assessed the

SUVmax in the main lesion. We compared PET/CT results with other imaging tests individually, even in patients submitted to different exams. The evaluation of axillary lymph nodes was also limited because we did not investigate the outcome of this finding regarding the performance of biopsy or axillary resection. Conventional imaging information was obtained from radiology reports because images were not available for analysis in many cases. Detailed information on the pattern of metastasis or recurrence was also not available. In addition, this study was performed at a single cancer center.

However, the results presented herein confirm that 18F-FDGPET/CT in the prone position has high sensitivity for the evaluation of invasive breast carcinoma and can be used as an additional and complementary method for the evaluation of these patients, even showing prognostic value, and contribute to more individualized therapeutic decision-making. Currently, 18F-FDG is the most widely used radiopharmaceutical for the evaluation of breast cancer based on the affinity of cells with increased glycolytic metabolism[21]. However, there are other radiopharmaceuticals, such as 18F-fluoroestradiol ([18F] FES), an estrogen analog that shows affinity for nuclear estrogen receptors[22,23], and ERα, an important prognostic biomarker of breast cancer[24]. The hybrid MRI and PET method can also be very promising in the evaluation of breast carcinoma, since it combines the molecular sensitivity of PET with the high-contrast anatomical MR image and its functional resources in a single PET/MRI examination[9].

CONCLUSIONS

FDG PET/CT with a dedicated breast protocol showed high sensitivity for the evaluation of patients with breast carcinoma in our sample, demonstrating a good correlation with other imaging methods, especially breast MRI. Our study suggests that the SUVmax value obtained from PET/CT in the prone position correlates with histological factors associated with tumor aggressiveness, subtype and overall survival and can be used as a prognostic biomarker in patients with breast cancer.

AUTHOR´S CONTRIBUTIONS

CCT: Conceptualization, Methodology, Investigation, Project administration, Data curation, Writing – review & editing. ENPL: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. RABM: Investigation, Validation, Visualization, Writing – review & editing. EFM: Investigation, Validation, Visualization, Writing – review & editing. AGVB: Conceptualization, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – review & editing.

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CASE REPORT
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Low-grade carcinoma *in situ* in fibroadenoma: a case report

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ABSTRACT

Fibroadenomas are the most common benign breast neoplasms. In rare cases, a carcinoma may develop within a fibroadenoma. The aim of this study was to report a case of low-grade carcinoma *in situ* in a fibroadenoma. A 31-year-old female, G0P0A0 and without family history of cancer, arrives at the service with an expressive breast lump growth along the year year. Core biopsy, histopathological and immunohistochemical studies showed an in-situ carcinoma in a fibroadenoma. Surgical resection was performed with a safety margin, and anatomopathological study and immunohistochemistry of the surgical specimen confirmed the core biopsy diagnosis. Currently, the patient is under annual clinical follow-up with mammography and breast ultrasound and no evidence of neoplastic disease. Although this is a rare event and few cases are described in the literature, carcinomas *in situ* can occur in a fibroadenoma.

KEYWORDS: breast neoplasms; breast carcinoma in situ; fibroadenoma; case reports.

INTRODUCTION

Fibroadenomas (AF) are the most common benign tumors of the breast and usually occur between the second and the third decades of life. They are mixed neoplasms with epithelial and stromal components. Breast carcinomas rarely develop within an AF. The frequency of malignancy of the epithelial component of AF is low (0.3%), usually with good prognosis. Whether the presence of an AF is a risk factor for breast cancer remains unclear. Cases of malignancy within an AF are more common in carcinomas ***in situ*** than in invasive breast cancers[1]. The conduct in these cases depends on whether the cancer is invasive or *in situ*[2].

The aim of this study is to report the case of a low-grade carcinoma *in situ* in an AF.

CASE REPORT

A female patient, 31-year-old, G0P0A0 and no family history of cancer, had noticed four years ago a lump in her left breast that had grown from 1.7 to 3.5 cm in the last year. Upon clinical examination, she had a palpable nodule in the upper lateral quadrant of the left breast measuring approximately 3.0 cm in diameter, and no lymph nodes suspected of neoplastic involvement in the ipsilateral axilla. Ultrasonography showed a solid, hypoechoic nodule, larger in the horizontal axis, with defined contours, without flow on Doppler and no calcifications (BI-RADS® 3).

Core biopsy and histopathological study were indicated due to the recent growth in the nodule, and showed atypical intraductal epithelial proliferation, apocrine metaplasia and stromal fibrosis. Immunohistochemistry showed positive cytokeratin 5/6 in myoepithelial cells, positive p64 in myoepithelial cells, negative CD34, Ki67 10%, negative protein s-100, positive vimentin in the stromal component — results consistent with carcinoma *in situ* in an AF. Resection was performed with a safety margin of 1.0 cm and reconstruction with local flap and intraoperative freezing of margins, which were negative. Histopathological examination of the surgical specimen showed a low-grade ductal carcinoma *in situ* (DCIS) developing within an AF (Figure 1). The anatomopathological examination showed atypical intraductal proliferation in AF, 3.8 cm tumor. Immunohistochemistry results: estrogen receptors (ER)+(90%), progesterone receptors (RP)+(90%), negative human epidermal growth factor (HER2) type 2 receptors (0-1), Ki-67 of 20%, positive cytokeratin in few isolated cells and absent in some ducts, and positive E-cadherin. The patient evolved well postoperatively.

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The possibility of a genetic panel to detect high penetrance germline mutations was discussed, but the patient chose not to perform it due to the low risk of *de novo* mutation and no history of cancer in her family. Annual clinical follow-up or adjuvant treatment with tamoxifen and radiotherapy was proposed. The patient opted for annual follow-up with mammography and breast ultrasound. Currently, the patient has no complaints and no evidence of recurrence on mammography and breast ultrasounds, being followed-up for approximately four years.

This study is part of a project conducted with cancer patients approved by the Research Ethics Committee of Universidade Estadual do Piauí (UESPI) — opinion number 4,311,835 (Certificate of Presentation of Ethical Appreciation: 30154720.0.0000.5209). The patient signed an informed consent form.

DISCUSSION

A breast carcinoma rarely develops within an AF. In the literature, there are about 250 cases described[3], being <15% invasive cancers (about 11% are invasive carcinomas of no special type (NST) and 3.4% are lobular invasive carcinomas), and the remainder intracellular carcinomas[1]. This case presented itself as a breast nodule with benign characteristics that increased in size, so a diagnostic investigation was indicated. Ultrasound and clinical examination results were compatible with an AF or a benign phyllodes tumor. After anatomopathological study by biopsy, the hypothesis of a carcinoma *in situ* was raised (unusual presentation at this age and with a palpable nodule — carcinomas *in situ* usually present initially with clustered microcalcifications or segmental distribution).

DCIS, also called intraductal carcinoma, is a neoplasm that does not invade the basement membrane. The breast carcinoma *in situ* develops within the ductal system, often in the terminal lobular duct unit[4]. It lacks the ability to spread through the body and is non-lethal. But its presence indicates a higher risk of invasive cancer if left untreated.

While AF occur more frequently in women aged 20 to 30 years old, carcinomas that develop within an AF occur mostly in women in the fourth decade of life[1,5], which is at odds with the patient reported in this case, as she was 31 years old at diagnosis.

In fact, it is not known for sure whether an AF is a risk factor for breast cancer. Dupont et al. reported a risk of developing invasive breast cancer 2.17 times higher in patients with AF and 3.10 times higher in patients with AF with complex changes[5]. However, other studies have attributed the increased incidence of breast cancer within an AF to selection bias[6]. It is known, however, that the rates of malignancy of the epithelial component of an AF are very low, between 0.002% and 0.3%.

In addition, during diagnosis, radiological findings are often non-specific for malignancy and may appear to be benign. New ultrasound techniques can show more characteristics of malignant lesions, such as shear wave elastography. This technique provides information on the elasticity of soft tissue components and can better characterize the risk of malignancy of breast nodules, especially those classified as BI-RADS® 3, avoiding unnecessary biopsies[7]. Shear waves propagate laterally, creating an elasticity map by measuring the parameters of lateral wave propagation. In the present case, elastography was not performed.

In this case, immunohistochemistry revealed epithelial malignancy, such as positive cytokeratin 5/6 and the presence of vimentin in the stromal component. Biomarkers RE/RP were positive and HER2 receptors were negative.

Therapeutic options for this type of carcinoma include conservative surgery with safety margins (at least 2 mm) or mastectomy — depending on the extent of the tumor and the relation between tumor size and breast size —, and adjuvant treatment with radiotherapy and hormone therapy in cases of RE/PR+[8], as discussed with the patient.

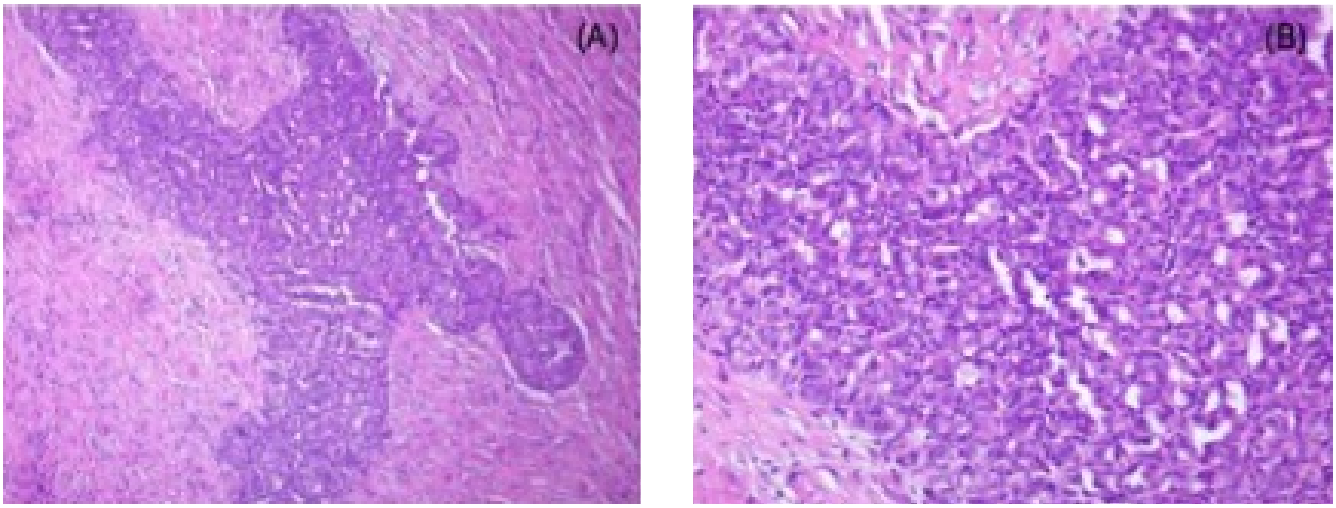

Figure 1. Low-grade carcinoma *in situ* in fibroadenoma – Hematoxylin-eosin. (A): 100x magnification. (B): 400x magnification.

CONCLUSIONS

Carcinomas *in situ* can occur in AFs, although they are a rare event and few cases are reported in the world literature.

AUTHORS' CONTRIBUTION

CQF: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. REARC: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. DRSF: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. ACMRLS: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. RGSJ: Conceptualization, Data curation, Formal analysis, Project administration, Writing – review & editing. ALNA: Conceptualization, Data curation, Formal analysis, Project administration, Writing – review & editing. SCV: Conceptualization, Data curation, Formal analysis, Project administration, Writing – review & editing.

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REVIEW ARTICLE
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Breast-conserving treatment in oncoplastic times: indications, cosmesis, and quality of life

Idam de Oliveira-Junior[1,2], Raphael Luiz Haikel[1], René Aloísio da Costa Vieira[2,3]*

ABSTRACT

Breast-conserving treatment was established as an oncologically safe procedure for breast cancer. However, the cosmetic outcomes of breast-conserving treatments are often unsatisfactory. In this scenario, oncoplastic breast-conserving surgery incorporated plastic surgery concepts and techniques into the oncological treatment in order to ensure better cosmesis, thus increasing the indications for breast-conserving treatment. At the same time, oncoplastic breast-conserving surgery is usually presented as a generic term, which should be evaluated taking many aspects into account: indication, patient selection, the surgery itself, cosmetic quality, and quality of life — data that are still scarce in the literature.

KEYWORDS: breast neoplasms; mastectomy, segmental; conservative treatment; surgery, plastic; cosmetic techniques.

INTRODUCTION

The surgical treatment of breast cancer is one of the only oncological areas in which other people besides the patient will judge the cosmetic outcome in the same way the oncologic result is assessed. The woman will have her breasts evaluated by radiotherapists, radiologists, gynecologists, mammography technicians, among others. Thus, we cannot address breast cancer surgery without its associated esthetic criterion[1].

For many years, radical mastectomy was the only surgical treatment offered for breast cancer. However, when Fisher et al. compared mastectomy, lumpectomy, and lumpectomy followed by breast radiotherapy in a randomized trial, they found no significant differences regarding disease-free survival, distant-disease-free survival, or overall survival among the 3 groups, even after 20 years of follow-up[2]. Likewise, between 1973 and 1980, Umberto Veronesi compared quadrantectomy associated with radiotherapy and mastectomy, and, once again, the results overlapped[3].

With the establishment of breast-conserving treatment (BCT) associated with the increase in early diagnosis, the advance in systemic therapies, and the consequent increase in patient survival, the analysis of surgical treatment transcended purely oncologic issues[4].

Surgeons started to look into improving the cosmetic quality of the procedure. After all, up to 30% of patients submitted to quadrantectomy need late reconstruction due to unsatisfactory esthetic outcomes[5]. Thus, oncoplastic breast-conserving surgery (OBCS) emerges to improve the cosmetic results of breast cancer surgeries. OBCS is usually presented as a generic term, involving procedures associated with both BCT and reconstruction after mastectomy. Nonetheless, it should be contextualized in each analysis and evaluated based on many aspects: indication, patient selection, the surgery itself, cosmetic quality, and quality of life (QoL) (Figure 1)[6].

Figure 2 illustrates the results between symmetry (Figures 2A and 2C) and bilateral surgery (Figures 2C and 2D), traditional surgery (Figure 2A and 2B) and OBCS (Figures 2C–2D), in addition to important breast tissue changes after radiotherapy, such as skin edema and fibrosis (Figure 2B), justifying the discussion on the subject.

ONCOPLASTIC BREAST-CONSERVING SURGERY

From an oncological point of view, OBCS allows initial candidates for radical treatment to receive conservative treatment. It enables large resections, with possible wider margins, which could lead to lower rates of positive margins without compromising esthetic results[6]. Many initial contraindications for BCT have become relative after OBCS, such as tumors larger than 5 cm and local skin infiltration, provided the margins are satisfactory and the breast volume allows the procedure.

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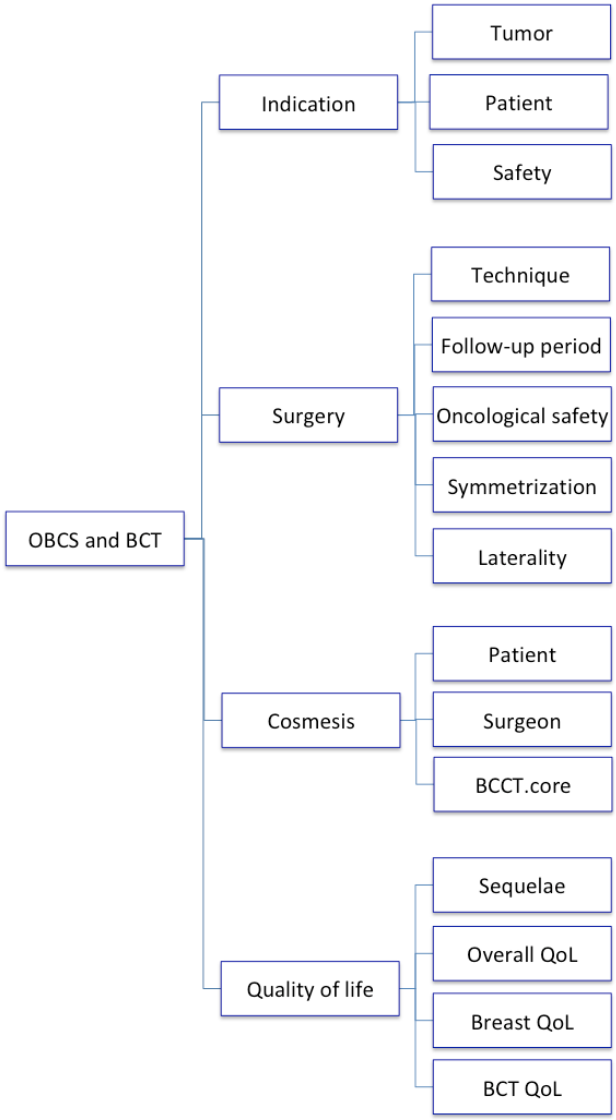
However, long-term follow-up data on recurrence, cosmetic results, or QoL are scarce[4].

Most published series evaluates the OBCS applicability to tumors that require a small surgical resection due to their reduced size. Silverstein et al. described the term "extreme oncoplasty" for cases with an initial indication for mastectomy, but that were submitted to OBCS. After assessing 66 patients with tumors whose mean size was 77 mm, they found similar recurrence to that of patients with small tumors[7].

Another factor contributing to a higher indication of BCT was the neoadjuvant chemotherapy for breast cancer, even in the presence of locally advanced tumors. Nevertheless, a good cosmetic result after surgery is expected by this group of patients. Thus, OBCS has achieved good cosmetic results even in more extensive resections of locally advanced carcinomas, representing a satisfactory option to avoid radical surgery, whose morbidity is higher[8]. Vieira et al. conducted a matched case-control study with a mean follow-up of 67.1 months, revealing that patients with locally advanced tumors submitted to neoadjuvant chemotherapy and OBCS showed no difference regarding local and locoregional recurrence and overall survival compared to BCT[4].



OBCS: oncoplastic breast-conserving surgery; BCT: breast-conserving treatment. Source: adapted from Oliveira-Junior et al. with authorization[6].

Figure 1. Outcomes involved in oncoplastic breast-conserving surgery.

Any patient eligible for breast-conserving surgery, with appropriate size and ptosis in relation to tumor size, should be considered a candidate for OBCS[9,10]. However, the selection of patients submitted to these procedures shows an important bias. They tend to be performed in young[11] and more educated patients, who might demand a better cosmetic result[4].

Several observational studies have evidenced the association between OBCS and lower rates of positive surgical margins. A recent meta-analysis by Losken et al. indicated that OBCS could halve the rate of positive margins (12% vs. 21%, p<0.0001)[12]. Consequently, it might reduce the rate of surgical re-excision, as shown by Down et al. (5.4% vs. 28.9%, p=0.002)[13]. Another meta-analysis involving 18 studies found no significant difference concerning reoperation between the OBCS and BCT groups after adjustment for publication bias[11].

Based on the assumption that the oncological safety of OBCS should be similar to that of standard treatment[14], Rietjens et al., in 74 months of follow-up, detected 8.4% recurrence in patients with pT2-3 tumors submitted to OBCS, whereas pT1 patients had no recurrence[15]. Another study identified local recurrence of 4.3% in OBCS and 3.7% in BCT[16]. Clough et al. found a 5-year cumulative incidence of 2.2%, 1.1%, and 12.4% for local, locoregional, and distant recurrence, respectively[17]. We emphasize that tumors are approximately 3 cm in size in most series that evaluate OBCS[4,17].

A meta-analysis including 11 studies compared the oncologic results between BCT and OBCS, with a total of 3,789 cases (2,691 patients in the BCT group and 1,098 in the OBCS group) without significant difference between pathological staging, and found that local and distant recurrence rates were similar in both groups. Overall survival data also revealed non-inferior effects of OBCS compared to BCT[18].

In a meta-analysis involving 18,103 patients with mean follow-up time ranging from 1.5 to 9.2 years, Kosasih et al. found no significant difference between BCT, OBCS, and mastectomy (relative risk — RR = 0.861; 95% confidence interval — 95%CI 0.640–1.160; p=0.296) regarding recurrence[11].

The comparison between BCT and OBCS in 8,659 patients (3,165 in the OBCS group and 5,494 in the BCT group) showed that the surgical specimen weight and the tumor size were higher in the oncoplastic group (2.7 vs. 1.2 cm), which also presented significantly lower positive margins and re-excision rates. Nonetheless, local recurrence was 4.2% in the OBCS group and 7% in the BCT group (p<0.0001), although follow-up was longer in the BCT group (64 vs. 37 months)[12].

SURGICAL TECHNIQUES AND STRATEGIES

OBCS incorporated plastic surgery concepts and techniques into the surgical treatment of breast cancer, becoming associated with the excision of breast parenchyma and the simultaneous reconstruction/reshaping of the defect in order to avoid local deformities. Therefore, a variety of techniques can be performed in BCT, extending its indications. In addition, by reducing the parenchyma, oncoplastic techniques promote the effectiveness of radiotherapy in the remaining tissue, with dose homogeneity and acceptably low complication rates[19,20].

In our field, Andrade Urban developed a classification based on technical skills to improve the training of surgeons. It consists of three distinct skills:

- Class I covers glandular mobilization and reshaping, without requiring specific surgical training;
- Class II demands specific training because it involves skills related to breast reconstruction with implants, mastoplasty, and mastopexy, usually bilateral for symmetrization;
- Class III encompasses autologous flaps or a combination of techniques, requiring specific training[21].

Other classifications for oncoplastic procedures have been proposed. The one by Clough et al. divides the technique into two levels, based on the complexity of the procedure. "Level 1" techniques are based on glandular mobilization and repositioning of the nipple-areola complex, with less than 20% of the breast volume resected. Those classified as "level 2" involve resections ranging from 20% to 50% of the breast volume and are divided into volume repositioning techniques (therapeutic mammoplasty) and volume replacement techniques (fascia or myocutaneous flaps), associated or not with contralateral mammoplasty[8,22]. The American Society of Breast Surgeons, in consensus, also opted for this definition and classification system of OBCS based on anatomy and volume, as it applies to most techniques described in the literature. However, the classification should act as a practical guideline for surgeons rather than a strict rule, as underlined by the committee[23].

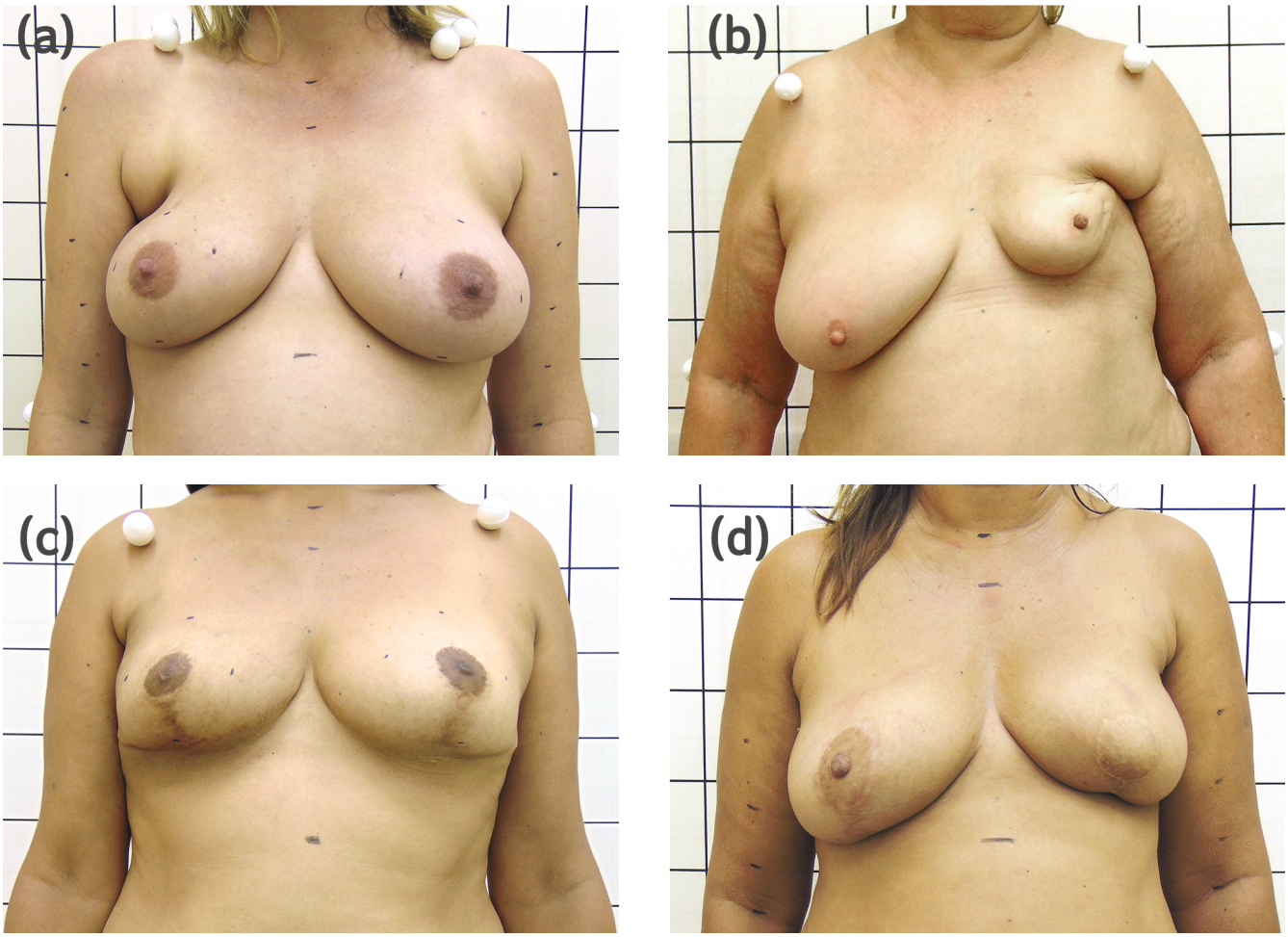


Figure 2. Breast-conserving treatment. (A) Symmetry and conservative treatment on the right breast; (B) asymmetry and conservative treatment on the left breast; (C) good symmetry in conservative treatment and symmetrization (D) asymmetry in conservative treatment with oncoplastic technique — plug flap — and symmetrization.

Training schools have divergences as to OBCS classification. In the "First International Consensus Conference on Standardization of Oncoplastic Breast Conserving Surgery", experts, mostly Europeans, voted to adopt the Clough classification as the standard for clinical practice (indication, planning, and performance of the procedure)[24]. Nonetheless, for billing purposes, the consensus was to use the classification by Hoffmann et al.[25], which is based on the complexity of the breast surgical procedure, whether oncologic, oncoplastic, or reconstructive. Still, they disagreed on which classification should be recommended as the best standard for clinical research[24].

Weber et al. proposed nomenclature and algorithms to help surgeons standardize the ideal OBCS procedure. The procedures were classified as conventional tumorectomy (glandular reapproximation and direct closure of the surgical wound), mastopexy (non-oncological skin resection and nipple repositioning, with or without pedicles), oncoplastic tumorectomy (glandular reshaping and volume replacement), and oncoplastic reduction mammoplasty (non-oncological breast reduction, with repositioning of the nipple-areola complex through pedicles). The two proposed algorithms — indication and reconstruction — are targeted at surgical planning according to breast size and shape, tumor size and location, vascular supply to suggest flaps, glandular reshaping, and specific pedicles to replace the resected volume[26].

Regardless of the classification adopted, conservative treatment involves class I and II procedures, favoring the training of mastologists and the development of centers directed at this training in Brazil[27].

Whether OBCS falls within the competence of the mastologist, surgical oncologist, or plastic surgeon is debatable. In Brazil, similar to other countries, professionals participate cooperatively in most cases. Nonetheless, this scenario can differ significantly: most women undergoing surgical treatment of breast cancer do not have access to reconstruction. Each surgical specialty has its usual advantages, but training should be required for OBCS to ensure oncological safety and superior cosmetic outcomes[21].

The surgeon must choose the surgical technique taking into account the tumor characteristics and the breast morphology, besides the developed expertise, not forgetting the patient's cosmetic expectations, considering the lack of a single formula for the surgery. Breasts vary considerably, resulting in several possibilities to solve the challenges posed by the tumor[4].

Regarding BCT, given the diversity of procedures, several authors have attempted to exemplify them based on breast volume[28], quadrant location[22,29], technique selected according to algorithms[24], variety of techniques[30], development of new techniques[10,31], and application to extensive surgeries[7]. Thus, the large number of techniques, ranging from small local parenchyma reshaping to elaborate resections, made the term OBCS very generic, combining various possible surgical outcomes, with different levels of complexity, into a single category. In this respect, several techniques are grouped, and given the lack of a standard, the literature has room for analyses and comparisons. Moreover, the theoretical-practical concept of oncological safety associated with the cosmetic result is recent and needs improvement[4,10].

Therefore, in BCT, oncoplasty involves care related to oncological treatment versus adequacy of the volume in the affected breast associated with the secondary adequacy of the volume in the contralateral breast[1]. Breast-conserving surgery often results in breast asymmetry, which is related to worse postoperative QoL and worse psychosocial functions; after all, the cosmetic result has become an important factor in the surgical treatment of breast cancer[32]. Women with significant breast asymmetry are more prone to a poorer psychosocial status than those with small asymmetry[33]. In order to maintain symmetry, many patients are submitted to oncological treatment involving OBCS and contralateral symmetrization in the same procedure; however, the literature on the subject is scarce, precluding any conclusions regarding its actual impact on women.

The ideal timing for contralateral breast surgery is after the end of radiotherapy in the index breast, considering the different degrees of volume and elasticity loss and of fibrosis. The index breast volume will continue to change progressively over the years due to the persistent radiation injury. Therefore, the asymmetry assessment should also consider the treatment duration and the moment of symmetrization[34].

After learning the long-term effects of radiotherapy and the varying degrees of asymmetry, many patients choose to undergo symmetrization and oncological treatment simultaneously; however, the need for symmetrization lacks criteria. In general, the literature has no objective data on the subject, and several authors do not describe the symmetrization rate, which should be part of studies related to BCT and OBCS[34].

COSMESIS ASSESSMENT

The main objective of breast-conserving surgeries is to have local control from an oncological perspective, preserving cosmesis. Nevertheless, surgical resection without adequate reshaping of the remaining parenchyma allows scarring and fibrosis to reveal, after radiotherapy, the unreconstructed cavity, the distortion of the nipple-areola complex, and the uniformity of the parenchyma distribution, which are factors OBCS has overcome[34,35].

Radiotherapy can cause immediate-to-late alterations, including skin depigmentation, telangiectasias, edema, fibrosis, and changes in breast sensitivity, varying according to dose, irradiated volume, and individual radiosensitivity. In general, combining these changes leads to a progressive reduction in breast volume, affecting the "time" aspect when evaluating breast cosmesis[36].

OBCS paradigms (oncologic principles associated with plastic improvement) are widely adopted; however, the lack of randomized data makes breast surgeons accept an increasing number

of series[26]. Tenofsky et al., *apud* Kosasih et al., when analyzing cosmetic satisfaction among patients submitted to OBCS and BCT, noted that 13.8% (OBCS group) and 7.1% (BCT group) were dissatisfied, although without statistical significance (p=0.191)[11]. In other evaluations, satisfaction with the cosmetic result is higher in the OBCS group than in the BCT one (89.5% vs. 82.9%, p<0.001)[12].

The main factors associated with breast asymmetry after BCT are age over 60 years, high body mass index, large tumor size, tumors located in the central, inner, or lower quadrants, small breast volume, need for re-excision, breast parenchyma resection greater than 100 cm^3, and radiation dose heterogeneity[34,35]. However, in a cohort of 1,035 patients, these factors did not negatively influence the esthetic result. The study showed that wound infection, pain, scar expansion, scars perceptible on palpation, and keloids were associated with a lower cosmetic classification[37].

Motivated by asymmetry, many patients undergo reconstructive procedures. After this procedure, for example, 94.5% of patients were satisfied after 1 year and 88.8% after 5 years, while 19.1% and 6.4% required a second and third surgery, respectively[38]. Of note, the cosmetic result may vary during the post-treatment follow-up since the late effects of radiotherapy mentioned above and the change in body mass may directly affect the satisfaction with cosmesis and breast symmetry.

Given the diversity of the procedures available, many cosmetic outcomes can be expected after BCT and OBCS. Thus, the cosmetic evaluation after breast-conserving procedures is relative, with poor rater agreement, which can be minimized after consensus among them. Nonetheless, this scenario hardly occurs in clinical practice[39].

Cosmetic results can be assessed with objective and subjective tools. Subjective methods take into account the analysis of professionals involved in the treatment, the patient's evaluation, or domains of QoL questionnaires[39-41]. In turn, objective methods consider the measurement of asymmetry between the treated and untreated breast, but there is no universal reference measure. In this scenario, the Breast Cancer Conservative Treatment Cosmetic Results (BCCT.core) software was created to evaluate patients submitted to BCT, using symmetry algorithms, with results calibrated by European experts, showing a great correlation between them. The results are divided into 4 categories (1-excellent, 2-good, 3-fair, 4-poor). This methodology is reproducible and widely used in research[42]. Nevertheless, the software is not available to the general public, with use only in research.

Regarding the effects of radiotherapy in BCT, the Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer (RTOG/EORTC) scale evaluates cutaneous and subcutaneous changes, while the Late Effects Normal Tissue Task Force/Subjective, Objective, Management, Analytic (LENT/SOMA) scale quantifies telangiectasia, fibrosis, edema, ulceration, breast pigmentation changes, lymphedema, and breast pain, with scores ranging from 0 to 4[43].

The cosmetic results of breast surgery have other forms of evaluation[44]. The Harvard scale, proposed by Harris, initially aimed at evaluating cosmesis after radiotherapy, assessing three main points: skin changes, breast fibrosis/retraction, and radiation-induced alterations, as well as cosmetic evaluation (excellent, good, fair, and poor)[45]. The Garbay scale, which evaluates the results of patients submitted to breast reconstruction[46] and was later used for patients undergoing BCT[32], analyzes breast volume, shape, and height, the inframammary fold, and scarring. It is grouped into four classes and assessed by the numerical sum of the results. The scale by Fitoussi et al. categorizes breast asymmetry and defines a reconstruction classification for contralateral symmetrization[38].

Despite the different classifications, no consensus has been reached on how to evaluate breast cosmesis after BCT. When comparing BCCT.core with the Harris scale, the results showed a poor association (Kappa=0.34)[42]. In turn, OBCS showed excellent results both in the Harris classification and the BCCT.core. Conversely, several series presented poor agreement between objective and subjective methods and the patient's self-report (usually the patient has a better self-evaluation compared to other methods)[32].

QUALITY OF LIFE

Compared to mastectomy, the benefits of breast-conserving surgery are indisputable, particularly because it ensures feminine fulfillment by preserving the normal breast sensation and limiting morbidity in relation to reconstruction by autologous implants or flaps. These benefits increase when adjuvant radiotherapy is administered after mastectomy with reconstruction[9]. Several studies have shown the advantages of OBCS when it comes to better cosmetic results and patients' satisfaction, although contradictory results have also been reported[12].

For the vast majority of surgeons, OBCS is strongly associated with improved QoL, but combining the cosmetic result and its benefits from the patient's perspective is quite complex[12,24].

With the increase in survival, concern with QoL has become routine in oncological treatment for both professionals and patients. Some questionnaires assess the general conditions of oncological treatment (e.g., European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire – EORTC QLQ C30, Functional Assessment of Cancer Therapy-General – FACT-G), others are specific for breast cancer (e.g., EORTC QLQ BR23, Functional Assessment of Cancer Therapy-Breast – FACT-B), mastectomy and breast reconstruction (MAS, Michigan Breast Reconstruction Outcome Study – MBROS, BREAST-Q), and BCT (Breast Cancer Treatment Outcome Scale – BCTOS, BREAST-Q)[40].

EORTC QLQ-C30 is a general questionnaire for cancer patients. It consists of 30 questions divided into 3 dimensions: functional scale, symptom scale associated with 6 unique items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial

difficulties), and overall QoL. Like QLQ-C30, QLQ-BR23 scores are converted from 0–100 and follow the same reasoning for interpretation. EORTC QLQ-BR23 is a QoL questionnaire specific to breast cancer patients. Validated in Portuguese, it has 23 questions divided into 2 dimensions — functional scale and symptom scale — and uses a 4-point scale to obtain the score (not at all, a little, quite a bit, and very much)[47].

Comparing the QoL of 485 patients submitted to BCT, 46 to mastectomy with immediate reconstruction, and 87 to mastectomy without reconstruction 1 year after treatment using the QLQ-C30 and QLQ-BR23 questionnaires, those who underwent BCT and immediate reconstruction showed better scores as to social function, general function, and body image. At the same time, the comparison of these two groups (BCT and reconstruction) presented no difference regarding objective cosmetic effects, except for body image in QLQ-BR23[48]. Another study used the QLQ-C30 and QLQ-BR23 questionnaires to assess the QoL of patients submitted to BCT (n=76) and to mastectomy without (n=20) and with (n=16) reconstruction. The authors identified that those who underwent BCT had better body image and were more satisfied than the other groups[49].

BCTOS[50], aimed at the subjective evaluation of esthetic and functional results after BCT, has questions about functional status, cosmetic status, breast-specific pain, and edema. It comprises 22 items — 8 questions related to breast shape and volume, 7 to shoulder/arm movement, 4 to arm volume, and 3 to breast pain and sensitivity[33]. These questions are scored from 1 to 4 points — 1 point meaning no difference between the treated and untreated breast or area and 4 points corresponding to a great difference between the treated and untreated breast or area. This questionnaire was translated into Brazilian Portuguese and validated[41].

BCTOS has proven to be effective in patients submitted to conservative treatment associated with radiotherapy[50]. BCTOS cosmetic results were compared with those of BCCT.core with high agreement, but patients presented higher rates of cosmetic satisfaction in BCTOS than in the software[51].

Another questionnaire developed is the Breast-Q, initially designed to evaluate breast surgery[52] and used in both plastic and reconstructive surgery. It is divided into six domains: satisfaction with breasts, general outcomes, care experience, psychosocial, physical, and sexual well-being. The second version of this questionnaire, created to evaluate BCT, has not been translated into Brazilian Portuguese yet, with few studies using it[53]. The literature has validation studies of the electronic version[54] and for the Japanese population, but not for a Brazilian version.

International study administering Breast-Q to patients submitted to mastectomy with and without reconstruction and to BCT revealed that the mastectomy with reconstruction group had better scores in the sexual well-being domain than the BCT and mastectomy without reconstruction groups. However, no difference was found in the psychosocial domain[55]; therefore, immediate reconstruction is related to better Breast-Q scores[56].

In the literature, comparing objective results evaluated by objective and reproducible QoL instruments has proven to be difficult. Exner et al.[57] used the Breast Analyzing Tool (BAT) to objectively evaluate the breast symmetry of 101 patients submitted to BCT, correlating the results with the QoL measured by the Breast Image Scale (BIS) and the EORTC QLQ-BR23. They found no direct association between symmetry and the patients' QoL.

The level of satisfaction does not necessarily reflect the degree of symmetry: women with normal breasts may be dissatisfied with them[58]. In general, QoL studies are not associated with objective results, and selection bias might occur when evaluating patients submitted to OBCS. Despite the apparent similarity between groups, previous choices have been made, leading to the selection of younger, better educated, and more inquisitive patients for OBCS.

By comprising a wide range of oncological and reconstructive surgical procedures, oncoplastic surgery — with or without symmetrization — allows the reduction of both the affected and the contralateral breast, which can be performed immediately, in stages, or later, with no differences in QoL between groups[59]. We underline that the patient's analysis of these results requires a gold standard, and the current methods can vary considerably in both cosmetic and functional evaluation[60].

CONCLUSION

Oncoplastic surgery increased the indications for breast-conserving treatment while maintaining oncological safety. As a result, OBCS favors breast preservation, increasing female satisfaction, which can positively impact cosmetic and QoL results.

Research ethics

As a literature review, this study does not require evaluation by the Research Ethics Committee, according to Resolution 466/2012.

The patients authorized the use of their images in scientific publications by signing the Informed Consent Form of a study approved by the Research Ethics Committee of the Hospital de Câncer de Barretos, under number 782/2014.

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AUTHORS' CONTRIBUTIONS

I.O.J.: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, writing – review & editing. R.L.H.: conceptualization, writing – original draft, writing – review & editing. R.A.C.V.: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, writing – review & editing.

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REVIEW ARTICLE
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The impact of anesthetic techniques on breast cancer recurrence: a systematic review of clinical evidence

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ABSTRACT

Introduction: Surgery is the most effective treatment for breast cancer; however, several factors can impair the immune system during the perioperative period, including the anesthetic technique. Since metastasis is the leading cause of death, one of the treatment pillars is to prevent cancer progression. This systematic review will focus on the prospective clinical evidence available on anesthesia's role in favoring breast cancer recurrence. **Methods:** The Cochrane Library, Medline, Embase, LILACs, and Web of Science were electronically searched from inception through December 2020 for randomized controlled trials assessing the association of postoperative recurrence and survival with the use of regional anesthesia, opioids, anesthetic adjuncts, and general anesthesia during surgical resection of breast cancer. In total, 711 articles were retrieved. After title and abstract screening and full-text reviews, five randomized controlled trials were selected. **Results:** Two studies compared inhalation anesthesia with total intravenous anesthesia, while three compared general anesthesia with regional anesthesia and analgesia. There was no significant association between the anesthetic technique and local recurrence, metastasis, or survival. **Conclusion:** This systematic review did not find an association between the type of anesthesia performed and a higher breast cancer recurrence rate. Up to this time, there is no clinical evidence to support a specific anesthetic technique for malignant breast tumor resection surgeries.

KEYWORDS: breast neoplasms; recurrence; anesthesia.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women globally, with 1.7 million diagnoses every year[1] and second in line for the most common cause of cancer-related death[2]. Surgery resection treats a large number of malignant tumors; breast cancer is no exception. Early detection of localized or regional breast cancer can procure a 99%4-85% 5-year survival rate[3], with 97% of women in stages I or II experiencing surgery[4]. Therefore, perioperative management may interfere with oncological outcomes.

Several risk factors impair the immune system during the perioperative period[5]. Pain, blood transfusion, hypothermia, and anesthetic technique cause immunosuppression, allowing cancerous cells to migrate to distant organs[6] — even surgical manipulation can release micrometastasis into the circulation, along with the acute inflammatory response that extensive surgery entails[7].

Metastasis is the major cause of death in breast cancer patients, with a 30% incidence rate[8]: therefore, preventing recurrence is of paramount importance. A new era of research has emerged in the anesthesia field. Each anesthetic technique affects cancer cells in a particular way. Regional anesthesia reduces surgical stress, inflammatory response, and opioid consumption[9-11]. Local anesthetics (LAs) have shown antiproliferative and cytotoxic effects against *in vitro*[12] tumor cells. Sevoflurane suppresses the immune system by decreasing Natural Killer (NK) cells' activity, promoting T-lymphocyte apoptosis and increasing pro-inflammatory cytokines[13-15]. Opioids have a more complex role on cancer recurrence[16]: a low dose can elicit tumor growth via angiogenesis and down-regulation of the immune response, while high concentrations may curb tumor growth. The opioid receptors κ and μ act divergently, with the former promoting and the latter inducing a pro-inflammatory response[17].

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A myriad of retrospective studies suggests that volatile anesthetics and opioid anesthesia promote breast cancer recurrence compared to propofol-based and regional anesthesia[18-20]. Exadaktylos et al.[18] reported that women had a significantly lower risk of cancer recurrence if submitted to a combination of propofol and thoracic paravertebral block (TPVB) compared to balanced general anesthesia (GA) with sevoflurane and opioids. However, the anesthetic technique of choice for mastectomies is still debatable.

This systematic review focused on the clinical evidence available on the role of anesthesia regarding breast cancer recurrence. To the extent of our knowledge, it was the first to compare only prospective randomized control trials. We described the data and critically analyzed randomized clinical trials on the use of regional anesthesia, opioids, anesthetics adjuncts, and GA in patients undergoing breast cancer resection.

METHODS

This systematic review was conducted according to the Cochrane Handbook for Systematic Reviews and Interventions[21] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[22]. The study protocol was published on Open Science Framework,

Search strategy

We conducted an electronic search of the following databases (from inception through December 2, 2020): Cochrane Library and Cochrane Trials Register, Medline, Embase, LILACs, and Web of Science; no language limitation was enforced. Search terms included: "Breast Cancer", "Anesthetic Technique" or "Regional Anesthesia" or "General Anesthesia", "Propofol" or "Sevoflurane", "Disease Free Survival" or "Recurrence" or "Metastasis". The complete list of search terms is attached in the online Appendix 1. Manually, we performed a thorough search within oncological and anesthesia society websites, annals of congresses, and articles' reference lists. Ongoing clinical trials were also assembled by searching the combination "breast neoplasms" at https://clinicaltrials.gov/[23].

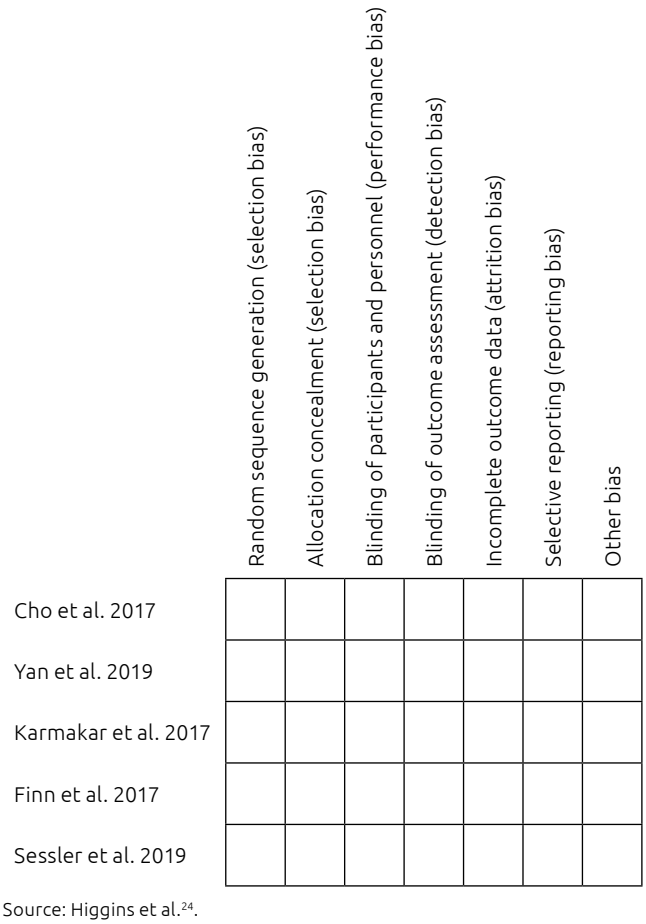
Study selection and data extraction

The inclusion criteria were threefold: randomized controlled clinical trials (RCT), surgery for resection of malignant breast tumor in female over 18 years old, and three possible interventions' scenarios — comparing the use of regional anesthesia, either isolated or combined to general anesthesia, with general anesthesia; comparing volatile anesthesia with total intravenous anesthesia; comparing opioid-free anesthesia with opioids. Studies depicting metastatic disease were excluded. The primary outcome was postoperative cancer recurrence, defined as locoregional recurrence and distant metastasis. The secondary outcomes were overall survival and recurrence-free survival.

Two of the authors (A.D., D.S.) independently assessed titles and abstracts for admittance into this review. If any divergence of judgment were manifested, a third author (A.A.) would settle. The data were extracted in a standardized way through an electronic form. Apart from measured outcomes and types of interventions, other extracted data included study-related information, such as author, year of publication, sample, follow-up time, and conclusions. Given methodological diversity and statistical heterogeneity, a meta-analysis was not conducted. Instead, a systematic review of the applicable clinical evidence was completed.

Risk of bias

We covered six domains for assessing the risk of individual bias[24]: selection bias, performance bias, detection bias, attrition bias, reporting bias, and others. A high risk of bias is considered when the studies fall out of these criteria. Two authors independently appraised these risks for the breast cancer recurrence outcome, which are summarized in Figure 1.



Source: Higgins et al.[24].

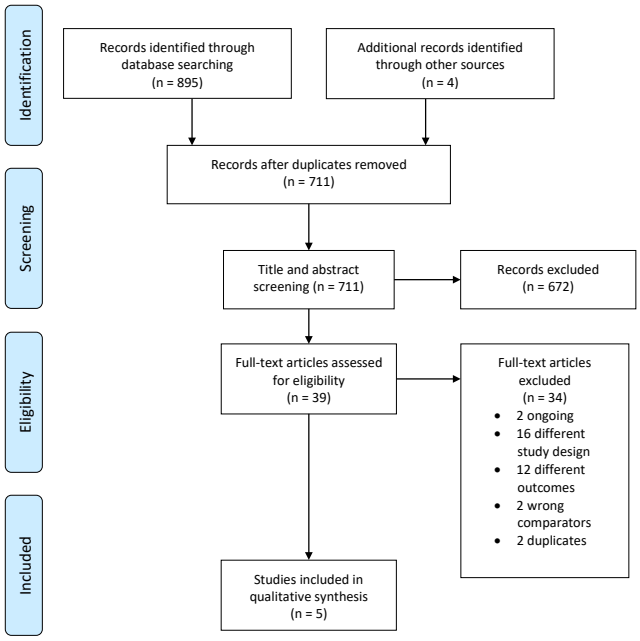
Figure 1. Risk of bias summary.

RESULTS

The electronic and manual search found 899 studies, 711 of them eligible for title and abstract review. Six hundred and seventy-two studies were deemed irrelevant, while 39 were singled out for full-text reading and quality assessment. Lastly, five clinical trials were selected for data extraction (Figure 2).

Two studies compared the association of inhalation anesthesia and total intravenous anesthesia (TIVA) (Table 1) on cancer recurrence rates, metastasis, recurrence-free survival (RFS), and overall survival (OS). Both included patients with breast cancer stage 0-III, and the type of surgery performed varied from breast-conserving surgery to radical mastectomy, with no significant difference between the groups. Cho et al.[25] followed 48 women for two years to find that only one patient in the sevoflurane-fentanyl (SEVO) group had a recurrence in the contralateral breast without statistical significance. Yan et al.[26] also investigated short-term cancer recurrence in 80 women for the same amount of time. The two-year RFS rate in the SEVO and TIVA groups for the first and second studies, respectively, averaged 89.5% and 97.6% (p = 0.138) while the two-year OS rate did 92.8% and 100% (p = 0.182).

The other three studies investigated cancer recurrence by comparing general anesthesia with regional anesthesia and analgesia (Table 2). Finn et al.[27] followed 54 women for five years — all underwent mastectomy with balanced GA and thoracic paravertebral block (TPVB), but, for 72 hours after surgery, one group received a perineural infusion of ropivacaine while the other received saline (placebo). No significant association between the anesthesia technique and cancer recurrence was observed. Karmakar et al.[28] followed 173 women for five years after a modified radical mastectomy and used a similar method of a continuous TPVB. The women were randomized into three groups: control, perineural infusion with saline (placebo), and perineural infusion with ropivacaine; all of them received total intravenous GA with propofol. Each group incidences of local cancer recurrence, metastasis, and all-cause mortality were 2.3% (95%CI 0.7–5.4%), 7.9% (95%CI 4.6–12.6%), and 6.8% (95%CI 3.6–11.2%), respectively. These studies did not discriminate in which breast cancer stage the patients were admitted.



Source: Shamseer et al.[22].

Figure 2. PRISMA flow diagram.

Table 1. Summary of trials comparing total intravenous general anesthesia versus balanced general anesthesia.

Author	Year	Study design	Tumor stage	Type of surgery	Intervention	Groups		Outcome	Follow-up time	Conclusion	Observations
						TIVA (n = 24)	*SEVO (n = 24)*				
Cho et al.[25]	2017	RCT	0-III	Partial mastectomy, total mastectomy, radical mastectomy	TIVA vs GA with volatile anesthetic	Propofol (TCI) + Ketorolac (60 mg)	Sevoflurane (according to BIS) + Fentanyl (50 mcg)	Incidence of cancer recurrence and metastasis	2 years	No significant association between anesthesia technique and recurrence was observed.	Both groups used remifentanil and tramadol.
						TIVA (n = 42)	*SEVO (n = 38)*				
Yan et al.[26]	2019	RCT	0-III	BCS, mastectomy with or without axillary lymph node dissection	TIVA vs GA with volatile anesthetic	Propofol 3-6 mg/kg/h	Sevoflurane 1.5-2% (according to BIS)	Incidence of cancer recurrence, RFS and OS	2 years	No significant association between anesthesia technique and recurrence was observed.	Both groups used fentanyl and flurbiprofen.

RCT: randomized controlled trial; TCI: target control infusion; TIVA: total intravenous anesthesia; SEVO: Sevoflurane; BIS: Bispectral index; RFS: recurrence free survival; OS: overall survival; BCS: breast conserving sugery.

Table 2. Summary of trials comparing general anesthesia versus regional anesthesia.

Author	Year	Study design	Tumor stage	Type of surgery	Intervention	Groups			Outcome	Follow-up time	Conclusion	Observations
Finn et al.[27]	2017	RCT	N/A	Unilateral or bilateral mastectomy with or without axillary lymph node dissection	General anesthesia + single dose RA vs GA + continuous dose RA	Control (n = 28)		LA (n = 26)	Incidence of cancer recurrence and OS	5 years	No significant association between anesthesia technique and recurrence was observed.	All patients received nitrous oxide, acetaminophen and intravenous opioid (fentanyl or hydromorphone or morphine)
						GA (sevoflurane) + TPVBs (ropivacaine 0,5% 15 ml + saline 72h)		GA (sevoflurane) + TPVBc (ropivacaine 0,5% 15 ml + ropivacaine 0,4% 72h)				
Karmakar et al.[28]	2017	RCT	N/A	Radical mastectomy	General anesthesia vs GA + single dose RA vs GA + continuous dose RA	*Control (n = 58)*	*Saline (n = 56)*	*LA (n = 59)*	Incidence of cancer recurrence, metastasis and OS	5 years	No significant association between anesthesia technique and recurrence was observed.	All patients received a propofol-based anesthesia
						TIVA (propofol)	TIVA (propofol) + TPVBs (ropivacaine 2 mg/kg + saline 72h)	TIVA (propofol) + TPVBc (ropivacaine 2 mg/kg + ropivacaine 0.25% 72 h)				
Sessler et al.[29]	2019	RCT	0-III	Simple mastectomy, modified mastectomy, wide local excision with node dissection	General anesthesia vs regional anesthesia	Control (n = 1,065)		LA (n = 1,043)	Incidence of cancer recurrence	36 months	No significant association between anesthesia technique and recurrence was observed.	Both groups used propofol, fentanyl and morphine
						GA (sevoflurane)		TPVB (bupivacaine 0.5% or ropivacaine 0.5% 10-20mL) + ropivacaine 0.1–0.2% 48 h)				

RCT: randomized controlled trial; GA: general anesthesia; RA: regional anesthesia; TIVA: total intravenous anesthesia; LA: local anesthetic; TPVB: thoracic paravertebral block (s: single; c: continuous); TEB: thoracic epidural block; OS, overall survival; N/A: not available.

The third study is a multicenter, prospective, randomized trial conducted by Sessler et al.[29]. Over two thousand women, initially classified as breast cancer stage 0-III, were accompanied for a median follow-up of 36 (IQR 24–49) months and divided into two groups: regional anesthesia-analgesia (n = 1,043) and general anesthesia and opioid analgesia (n = 1,065). The first group received a thoracic epidural or a paravertebral block with a continuous catheter infusion of local anesthetic for postoperative analgesia. In the second group, anesthesia was maintained with sevoflurane, and the patients received morphine sulfate at the end of the surgery. The groups reported 102 (10%) against 111 (10%) recurrences, respectively (HR = 0.97, 95%CI 0.74–1.28; P = 0.84), indicating that regional anesthesia did not reduce breast cancer recurrence.

A meta-analysis was not conducted due to the diverseness in general anesthesia techniques, local anesthetics used for TPVB, and tumor staging permeating each study.

DISCUSSION

Our research showed no significant statistical association between anesthetic technique and higher breast cancer recurrence rate. Since our review was limited to randomized clinical trials, only five studies could be considered, although a few ongoing clinical trials may publish results in the following years (Table 3).

We divided our findings into two groups: intravenous anesthesia versus volatile anesthesia and general anesthesia (GA) versus GA combined with regional techniques (Table 1). In the first group, neither study reported intervention-related benefits.

Table 3. Summary of ongoing clinical trials registered on Clinicaltrials.gov.

Trial number	Study Title	Interventions
NCT03109990	Impact of Dexmedetomidine on Breast Cancer Recurrence After Surgery	•Drug: Dexmedetomidine •Drug: Saline
NCT03941223	Regional Anesthesia for Breast Surgery	•Procedure: PECSII and paravertebral blocks
NCT01204242	IV Lidocaine for Patients Undergoing Primary Breast Cancer Surgery: Effects on Postoperative Recovery and Cancer Recurrence	•Drug: Lidocaine •Drug: Saline
NCT03117894	PECS-2 for Breast Surgery	•Procedure: PECS-2

PECS2: pectoral nerve block type 2.

This finding contradicts Wigmore et al.[30], who, in a 2016 retrospective study with over 7,000 cancer patients, reported an approximately 50% higher mortality rate for volatile anesthesia against intravenous anesthesia, with an adjusted hazard ratio of 1.46 (1.29 to 1.66).

Cho et al.[25] compared two groups with different anesthetic techniques and analgesia: a propofol-ketorolac group (TIVA) and a sevoflurane-fentanyl group (SEVO), investigating the effect of these techniques in the cytotoxicity of natural killer cells and tumor recurrence up to two years after surgery. Cancer metastasis did not occur in either group, in spite of different drug properties. Propofol has cyclooxygenase (COX-2) inhibiting activity, which reduces the production of prostaglandin E2 (PGE2), a mediator of pain and inflammation[31]. Ketorolac also impedes prostaglandin synthesis via the inhibition of the COX enzyme, above its antitumor and anti-angiogenic properties[32]. Volatile anesthetics and fentanyl, though, suppress NK cells and T lymphocytes[33,34].

Pain causes immunosuppression[35]; however, since both groups had a similar analgesic efficacy, the authors could eliminate it as a contributing factor. Pain scores were assessed using an 11-point numerical rating scale (NRS) at 30 minutes, 6 hours, 24h, and 48h postoperatively. If the patients complained of an NRS ≥ 4 pain, ketorolac and propacetamol were given to the TIVA group and fentanyl to the SEVO group. Since both groups received different analgesic drugs, the authors could not discriminate each drug's effects on inflammatory response. Another limitation of the study was that all patients received remifentanil intraoperatively and tramadol for postoperative pain control — even though they are not considered immunosuppressive drugs and the doses were equivalent between the groups[36,37], we cannot exclude their opioid effect.

Yan et al.[26] had a short-term recurrence rate of breast cancer in five (6.3%) patients, four SEVO and one TIVA, during 28 months of follow-up. Two deaths were observed, both in the volatile group. No difference was found between RFS (p = 0.953) and OS (p = 0.281) between the two anesthetic techniques. Propofol was used for anesthetic induction in both groups, and fentanyl and flurbiprofen were given to all patients to provide postoperative analgesia. Those interventions could make it difficult to differentiate the individual properties of sevoflurane and propofol in the immune response. However, the study aimed to compare different anesthetic techniques rather than just different drugs.

In both Cho's and Yan's studies, we found puzzling elements and could not observe benefits from either anesthetic technique. Besides, the short-term RFS of breast cancer was elevated[38], which would require a large sample and a longer follow-up to detect any significant difference.

Forget et al.[39] had already suggested that non-steroidal anti-inflammatory drugs (NSAIDs) given shortly before surgery produce antitumor effects. Fentanyl has also demonstrated antitumor properties by inhibiting cancer cell migration and invasion[40];

however, in a large Danish cohort population study, opioid use showed no clinically significant association with breast cancer recurrence[41]. Thus, the effects of opioids on tumor growth and metastasis are complex and controversial: they may play a beneficial role, but it depends on drug concentration, duration of exposure, and even cancer type[16,42].

In 2006, the first study to describe a positive relationship between regional anesthesia and breast tumor propagation, by Exadaktylos et al.[18], showed the recurrence rate for the sevoflurane-fentanyl group as four times higher than the propofol-paravertebral block group. On the other hand, Kairaluoma et al.[43], in 2016, published a similar retrospective study following 86 women for 12 years; the results did not demonstrate any anti-metastatic effect of perioperative regional anesthesia.

Our second group of studies, which analyzed regional techniques, culminated in findings analogous to Kairaluoma et al's. Karmakar et al.[28] compared TIVA with GA combined with TPVB and a third group that used postoperative transcatheter analgesia. There was no difference in the risk of local cancer recurrence, metastasis, or all-cause mortality between the groups ($p = 0.79$, $p = 0.91$, and $p = 0.13$, respectively). When compared to the group which received only GA, the risk of local recurrence or metastasis agreed with that for patients in the GA plus single-TPVB group (HR = 1.11, 95%CI 0.32–3.83) or the GA plus continuous-TPVB group (HR = 0.79, 95%CI 0.21–2.96).

Since all patients received total intravenous anesthesia with propofol, it is questioned whether this could camouflage the regional anesthesia technique's anti-inflammatory perk. As explained earlier, propofol has numerous documented positive effects on the immune system function[14,31,44], so that the TIVA components may have conferred this immunoprotective benefit. In contrast, using a single general anesthesia technique helped to evaluate how regional anesthesia affected the recurrence rate.

Finn et al.[27] concluded that adding a continuous ropivacaine infusion to a single-injection paravertebral block in the immediate postoperative period did not decrease the post-mastectomy cancer recurrence risk. Five out of 54 (9.3%) patients suffered from recurrence: three among those in the ropivacaine group (11.5%) and two in the saline group (7.1%; $p = 0.92$). Nevertheless, we should also consider that single-injection ropivacaine was administered to all patients, which might have decreased surgical stress in both treatment groups — ropivacaine can provide 8-16 hours of analgesia. Therefore, albeit not always an obvious choice, regional anesthesia is a technique with proven benefits; with the TPVB comes less chronic pain and better postoperative physical and mental performance[45].

Sessler et al.[29] was a much-expected multicenter trial. A large sample and well-designed study, it proved the irrelevance of the regional anesthetic technique in attaining less tumoral occurrence. Nonetheless, there is space for reservations, as has already been discussed[46-49]. Firstly, anesthetic techniques overlapped, with the concurrent use of fentanyl, propofol, and morphine in all patients and the supplementation of sevoflurane in 17% of the patients from the paravertebral block group. This combined use of opioids and volatile anesthetic with the regional technique might have interfered with its benefit. Secondly, the average follow-up of 36 months can be considered a short time to assess tumor recurrence. Finally, better screening and superior protocol regimens have decreased breast cancer mortality rates over the last decade[50], meaning the clinical treatment of the disease itself has evolved[51] during the total general study period of 12 years.

The temporary immune changes caused by anesthetic drugs do not seem to bring long-term repercussions. Despite the paucity of relevant randomized controlled trials, where just one avails a high level of evidence, our qualitative analyses did not find an association between the type of anesthesia performed and the prognosis in breast cancer patients. Neither regional nor total intravenous anesthetic techniques showed significantly superior outcomes when compared to general anesthesia.

Our research's primary limitations were the narrow set of applicable studies, the significant heterogeneity, the small sample size and short follow-up time from some trials, and the high or unclear risk of bias from most included studies. This type of review suffers from difficulty to standardize in order to reduce bias. It is impossible to blind the anesthesiologist who will administer distinct techniques. Besides, each trial adopted different doses and concentrations, and the disease itself bears multiple stages. The stage and grade of the tumors and the surgical management variables presented a good distribution among the study groups, but most women were diagnosed in the early stages, which naturally translates to fewer recurrence rates[3]. Due to this low incidence of recurrence, the validation of the findings might prove difficult, even with significant statistical differences. There are yet other questions that may raise bias for this type of controlled trial: does breast cancer surgery stress is enough to cause immunosuppression? Does the natural evolution of anti-cancer therapies inhibit the *in-vitro*-proved[52,53] harmful effects of anesthetics? Therefore, we suggest choosing the best available technique, considering patient comorbidities and particularities.

CONCLUSION

This review did not find an association between the type of anesthesia performed and the long-term prognosis in patients with breast cancer. It points out to no clinical evidence currently supporting a specific anesthetic technique for malignant breast tumor resection surgeries. However, the scarcity of high-quality randomized clinical trials on the subject, with larger samples and longer follow-up times demands further research.

AUTHORS' CONTRIBUTION

A.D.: conceptualization, investigation, methodology, data acquisition, formal analysis, writing – first draft, writing – review & editing; A.A.: conceptualization, investigation, methodology, data acquisition, formal analysis, writing – first draft; D.S.: conceptualization, investigation, methodology, data acquisition, formal analysis, writing – review & editing; J.L.A.: conceptualization, methodology, formal analysis, writing – review & editing.

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REVIEW ARTICLE
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Molecular breast imaging and background uptake of fibroglandular tissue as tools to predict neoplasms in dense breasts

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ABSTRACT

The sensitivity of mammography as a screening method is low in dense breasts, which are associated with a high risk of developing tumors. Thus, molecular breast imaging (MBI) with background uptake (BPU) of fibroglandular tissue can be used as a complementary method. The aim of this review was to synthesize the existing evidence on these important diagnostic imaging tools. Three electronic databases were searched to identify original articles, including publications dating from September 2010 and September 2020, in English, conducted in any location, and addressing at least one aspect related to dense breasts and Breast-specific gamma-imaging (BSGI). In total, 22 studies were reviewed. Several advantages of MBI and BPU as complementary methods of screening for dense breasts were found. Among them, we can mention the increase in breast cancer detection rate, easy implementation in clinical practice, high patient satisfaction, low cost and good reproducibility. In view of the good results found in our review, we can conclude that the implementation of MBI, especially with BPU, can be a promising complementary tool for screening of dense breasts.

KEYWORDS: molecular imaging; breast neoplasms; radionuclide imaging; breast density.

INTRODUCTION

Breast cancer is the type of cancer with the highest incidence among women around the world, with 2,088,849 new cases reported worldwide in 2018, which corresponds to 11.6% of all cases of cancer detected in that year[1].

Mammography is the standard screening method to detect breast cancer due to its high sensitivity in most cases, enabling diagnoses at the earliest stages and, therefore, reducing mortality rates. However, this method has some relevant limitations. One of them is the use in dense breasts, since the sensitivity of the mammogram decreases as the breast density increases.

Dense breasts are strongly associated with the risk of developing tumors. However, as this is a highly prevalent condition, it is impractical for physicians to consider that all women with this type of breast constitution are at high risk, as this would justify additional tests or preventive options in almost half of the female population. To identify the subset of women with dense breasts who are most at risk for breast cancer and who is most likely to benefit from these strategies, improved risk stratification tools are needed[2].

Molecular Breast Imaging (MBI), also known as Breast-specific gamma-imaging (BSGI), which is a nuclear medicine scan performed with the Sestamibi-99mTc radiotracer and a dedicated gamma camera, can be one of these tools. New technologies, including cadmium-zinc-telluride (CZT) detectors, silicon photodiodes, and small detectors placed in the configuration of a mammograph, allow to reduce so drastically the radiation dose to obtain images in this type of study that it has become acceptable as a screening exam.

In the assessment of dense breasts by magnetic resonance imaging (MRI), the level of gadolinium contrast enhancement within the fibroglandular tissue, termed Background Parenchymal Enhancement (BPE), has been associated with both prevalent and incident breast cancer. Similarly, the background uptake (BPU) of fibroglandular tissue in MBI depicts the level of Sestamibi-^{99m}Tc uptake in that tissue, and is also strongly associated with the risk of breast cancer[3].

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Given the current importance of BPU as a tool for screening cancer in dense breasts and the lack of studies on the subject, we decided to carry out an integrative literature review aiming to better guide the scientific community on the subject.

METHOD

The decision to carry out an integrative review was aimed at a potential view of studies carried out with different designs.

Data sources and research strategy:

To find articles in the literature, a search was carried out in the following databases: Web of Science, PubMed and Medical Literature Analysis and Retrieval System Online (Medline). The following strategy was used in both researched bases: (("molecular breast imaging" OR "MBI" OR "breast specific gamma imaging" OR "breast-specific gamma imaging" OR "BSGI") AND ("dense breast" OR "background parenchymal uptake" OR "BPU")).

Inclusion, exclusion and eligibility criteria

All studies included in this review met the following inclusion criteria:

- papers written in English and published between September 2010 and September 2020;
- studies conducted in any location;
- papers exploring at least one aspect related to dense breasts and scintigraphy performed in specific mammary gamma-camera.

Since the number of publications found on the topic was not large, quantitative, qualitative and mixed studies were included in the review. The exclusion criteria were:

- journal publications with impact factor less than 2;
- review or case report formats.

The following eligibility criteria were defined:

- papers that were specifically relevant to the topic addressed;
- publications that did not primarily address technical tools.

Selection and screening of articles

First, the title and abstract of the papers were evaluated by two authors as to the adequacy to the theme, using the inclusion and exclusion criteria. Then, articles selected for evaluation of the full text were independently reviewed by two authors, and then jointly in case of any discrepancies. A third author was consulted to resolve divergences and to assist in the final decision on whether to include or exclude the article.

Quality assessment

The critical evaluation of selected articles was made by two independent reviewers on the methodological quality. For quality assessment, two distinct checklists were used: the Critical Appraisal Skills Program (CASP) checklist for qualitative studies[4], and the Joanna Briggs Institute (JBI) checklist for quantitative studies[5]. A third reviewer was consulted to reconcile any discrepancies in quality assessments.

Data extraction and synthesis

Data extraction tables were created independently by two authors, and then modified as necessary (Tables 1 and 2). Information on these tables included author, year of publication, country, study characteristics, and main results. Data were extracted by one author and verified by two other authors for accuracy. A meta-analysis of quantitative studies was not feasible due to the heterogeneity of the studies' approaches to measure and report knowledge.

RESULTS

Summary of study selection

The search in databases identified 117 records. Of these, 24 were duplicates and were later removed. The initial screening process based on title and abstract resulted in the exclusion of 55 articles, leaving 38 for full-text reading. Then, another 16 articles were excluded, 14 for not focusing specifically on the topic and 2 for being technical tools. The search and selection process is shown in Figure 1.

Studies' characteristics

The 22 studies included in this review were published between 2011 and 2020 and conducted in 3 countries: the United States of America (n = 18), China (n = 2) and South Korea (n = 2). Table 1 shows their outstanding characteristics.

Quality of studies included

Study quality was rated as good (score ≥ 80), regular (score 50–79%), and poor (score <50%). Due to the limited literature available in this area, all studies were included in this review, regardless of their quality. However, none of them had a bad qualification.

Studies' results

The breast cancer detection rate is increased when MBI is associated with mammography[6,7], especially in cases of dense breasts[6]. In the study by Rhodes et al., when associating MBI with mammography, there was the detection of 8.8 cases of breast cancer per 1,000 women with dense breasts on mammography[6].

Other studies have shown that MBI was useful to predict whether breast lesions are malignant or benign, and found a high overall sensitivity in this type of study when it comes to detecting breast cancer (95.4%), with no significant difference considering non-dense and dense breasts, regardless of breast density assessed by mammography[8,9].

Table 1. Characteristics of the studies.

Author and year of publication	Location	Methodology	Sample
Hruska et al., 2018[2]	MayoClinic, USA	Case-control study Survey questionnaires Review of medical data	239 individuals
Hruska et al., 2021[3]	MayoClinic, USA	Retrospective cohort study Analyses of MBI studies with BPU assessment and medical data review	2,992 women
Rhodes et al., 2015[6]	MayoClinic, USA	Prospective study MBI Image Analysis	1,585 women
Brem et al., 2016[7]	The George Washington University Medical Faculty, USA	Retrospective study MBI and mammography image analysis	849 women
Choi et al., 2018[8]	Incheon St. Mary's Hospital, College of Medicine, South Korea	Retrospective study MBI image analysis Breast Biopsy Results	231 women
Rechtman et al., 2014[9]	The George Washington University, USA	Retrospective evaluation MBI image analysis Breast Biopsy Results	341 women (347 breast assessed)
Conners et al., 2012[10]	MayoClinic, USA	Observational study Observing MBI results	50 MBI exams
Rhodes et al., 2020[11]	MayoClinic, USA 2019	Qualitative study	NR
Shermis et al., 2016[12]	ProMedicaBreastCare Center, USA	Retrospective study MBI, mammography and MRI image analysis Breast Biopsy Results	1,696 patients
Shermis et al., 2017[13]	ProMedica Breast Care Center, USA	Qualitative study	NR
Zhang et al., 2020[14]	Hospital of Zhejiang University School of Medicine, China	Retrospective study Analysis of ultrasound, mammography and BSGI images	364 women
Yu et al., 2016[15]	Zhejiang University School of Medicine, Hangzhou, China	Retrospective study Analysis of MBI, mammography, ultrasound and MRI images	357 women
Rhodes et al., 2011[16]	MayoClinic, USA	Prospective study MBI and mammography image analysis Breast Biopsy Results	936 women
Hendrick et al., 2016[17]	Universidade do Colorado, USA	Retrospective study Use of data from Rhodes et al., 2015 Analysis of mammography, MBI and mammography associated with MBI.	1,595 women
Hruska et al., 2015[18]	MayoClinic, USA	Prospective single-institution study Review of mammography and MBI studies Determining the costs of breast exams	1,585 women
Hruska et al., 2016[19]	MayoClinic, USA	Retrospective case-control study Review of medical data and MBI images	241 women
Hruska et al., 2019[20]	MayoClinic, USA	Prospective study, pilot Review of medical data, application of questionnaires and analysis of MBI studies	21 women
Yoon et al., 2015[21]	EwaWomansUniversity Seul, South Korea	Retrospective study MBI, MRI and mammography image analysis Medical data collection	145 women
Ching et al., 2018[22]	The George Washington University, USA	Retrospective study MBI image analysis Breast biopsy results	153 women
Hruska et al., 2015[23]	MayoClinic, USA	Retrospective study Review of medical data, questionnaires MBI and mammography analysis	1,149 women
Hruska et al., 2015[24]	MayoClinic, USA	Cohort study Collection of medical data, measurement of hormone levels and analysis of MBI studies	42 women
Dibble 2021[25]	Alpert Medical School of Brown University, USA	Editorial comment	NR

NR: not reported; MBI: molecular breast imaging; MRI: magnetic resonance.

Table 2. Findings of the studies.

Author, year of publication, study design	Objectives	Interventions/ methods	Results/Conclusions
Hruska et al., 2018[2] Case-control study	To develop and evaluate a new quantitative method that assesses BPU, to compare quantification to qualitative categorization, and to determine the association of BPU with the risk of developing breast cancer.	The association of quantitative BPU with breast cancer was examined.	BPU quantification is a reproducible method that can predict the risk of breast cancer, as well as a qualitative method, regardless of the density seen on mammography and hormonal factors.
Hruska et al., 2021[3] Retrospective cohort study	To examine the association of BPU with breast cancer and estimate the absolute risk and discriminatory accuracy of BPU by means of a cohort study.	Categorization of patients according to BPU in MBI exams	BPU in MBI is an independent risk factor for breast cancer, with a strongest association among postmenopausal women with dense breasts.
Rhodes et al., 2015[6] Prospective study	To evaluate the diagnostic performance of MBI in the evaluation of women with dense breasts after alterations that reduced the radiation dose.	Decrease in radiation dose in MBI study.	The addition of low-dose radiation MBI to routine mammographic evaluation pointed to a 67% increase in sensitivity to detect neoplasms.
Brem et al., 2016[7] Retrospective study	To determine the increase in breast cancer detection when using MBI in conjunction with mammography to assess women at high risk for breast cancer.	NA	MBI increased breast cancer detection by 1.7% in the study, suggesting that it is beneficial for the detection breast cancer in high-risk women, particularly those with dense breasts.
Choi et al., 2018[8] Retrospective study	To investigate which feature of BSGI uptake in women who were recently diagnosed with breast cancer was associated with malignancy.	NA	Analysis of radiotracer uptake characteristics in BSGI is useful to predict whether breast lesions are malignant or benign.
Rechtman et al., 2014[9] Retrospective study	To evaluate the sensitivity of MBI for detecting breast cancer in dense and non-dense breasts.	NA	BSGI has high sensitivity for detecting breast cancer in women with dense and non-dense breasts and is an effective complementary imaging method for the assessment of breasts.
Conners et al., 2012[10] Observational study	To determine the diagnostic agreement and accuracy in the use of a lexical pattern of description in the interpretation of the MBI.	NA	Newly trained radiologists assessing MBI with the proposed lexical pattern achieved a high rate of agreement and diagnostic accuracy.
Rhodes et al., 2020[11] Qualitative study	To investigate whether the MBI exam has a route to supplemental screening for dense breasts.	NA	There is currently no consensus among specialists or imaging societies as to the need to use BPI or additional screening. Therefore, patients should be guided on the balance between benefits and harms.
Shermis et al., 2016[12] Retrospective study	To retrospectively assess the clinical performance of molecular breast imaging as a complementary screening tool for women with dense breast tissue.	NA	Molecular breast imaging linked to a high incremental cancer detection rate of 7.7% at an acceptable radiation dose.
Shermis et al., 2017[13] Qualitative study	To describe how MBI is used in conjunction with recent technological advances in other imaging methods for breast cancer screening and problem solving.	NA	The integration of MBI into clinical practice was proven simple, easy to implement, with high patient satisfaction and easy reimbursement.
Zhang et al., 2020[14] Retrospective study	To investigate the adjuvant efficacy of US and BSGI for dense breasts.	NA	For women with dense breasts, mammography plus BSGI or US may improve diagnostic accuracy. Furthermore, BSGI has high specificity and can reduce invasive biopsies.

Continue...

Table 2. Continuation.

Author, year of publication, study design	Objectives	Interventions/ methods	Results/Conclusions
Yu et al., 2016[15] Retrospective study	To analyze the diagnostic value of BSGI for Chinese women.	NA	BSGI may help improve the ability to diagnose early-stage breast cancer among Chinese women, particularly for ductal carcinoma in situ (DCIS), mammographically dense breasts, and non-luminal breast cancer A.
Rhodes et al., 2011[16] Prospective study	To compare the performance of dedicated gamma camera and mammography in screening women with dense breasts.	NA	The addition of gamma-camera imaging to mammography increased significantly the detection of node-negative breast cancer in dense breasts.
Hendrick et al., 2016[17] Retrospective study	To estimate radiation-induced cancer mortality for mammography and MBI based on the biological effects of reporting ionizing radiation VII in asymptomatic women with dense breasts aged 40 to 79 years.	NA	The radiation benefit-risk ratio is estimated at 13 for 40 to 49 years with mammography, and the value doubles for each subsequent age range, from 10 years to 70–79 years. For BSGI, this ratio is estimated at 5 for women aged 40–49 years and doubles at 70–79 years.
Hruska et al., 2015[18] Prospective study	To investigate the diagnostic gain and costs generated by adding MBI to screening mammography in women with dense breasts.	Adding MBI to mammography for screening of dense breasts	There was an increase in the overall costs and rate of benign biopsies, but also an increase in the rate of cancer detection, which resulted in a lower cost per case detected.
Hruska et al., 2016[19] Case-control study	To investigate whether BPU in MBI is a risk factor for breast cancer.	Associations between categories of BPU and risk of developing breast cancer	This study provided the first evidence of BPU as a risk factor for breast cancer.
Hruska et al., 2019[20] Prospective study	To explore the feasibility of offering a short-term low-dose oral tamoxifen intervention for women with high BPU and examine whether this intervention would reduce BPU.	Women with high BPU had an MBI exam, followed by another after 30 days of oral tamoxifen.	Short-term intervention with low-dose tamoxifen may reduce high BPU in MBI for some patients. Preliminary findings have suggested that 10 mg of tamoxifen per day may be more effective than 5 mg to induce BPU decline in 30 days.
Yoon et al., 2015[21] Retrospective study	To investigate factors that may affect MBI uptake in normal breasts and the impact of uptake on MBI diagnostic performance.	NA	BPE in RNM was the most important uptake factor in the MBI. High background uptake or marked background parenchyma enhancement can diminish MBI diagnostic performance.
Ching et al., 2018[22] Retrospective study	To evaluate the correlation between the characteristics described in the MBI and the positive predictive value in the detection of breast cancer.	NA	Neither mass or non-mass variation nor the assessment of background uptake in MBI were significant determinants of probability of malignancy. Dense breasts were associated with low predictability and heterogeneous background uptake in MBI.
Hruska et al., 2015[23] Retrospective study	To describe the prevalence of the BPU categories observed in MBI screening and to examine its association with mammographic density and other clinical factors.	NA	Among women with similar mammographic density, BPU ranged from photopenic to marked. The highest BPU occurred in young, non-menopausal patients on hormone therapy.
Hruska et al., 2015[24] Cohort study	To assess the impact of the menstrual cycle phase on the aspect of BPU.	MBI study in different phases of the menstrual cycle.	When high BPU was present, it was more often seen during the luteal phase compared to the follicular phase, and in women with dense breasts compared to non-dense breasts.
Dibble 2021[25] Qualitative study	Editorial comment regarding ARTICLE 20 [3]	NA	The results of the article in question add to the growing literature that supports personalized breast cancer screening and risk assessment incorporating imaging biomarkers.

NA: not applicable; MBI: molecular breast imaging; BPU: background uptake of fibroglandular tissue; BPE: background enhancement of fibroglandular tissue; US: ultrasound.

Among the advantages of MBI studies, we can highlight a high incremental rate of cancer detection at an acceptable radiation dose, easy integration to implement in clinical practice, with high patient satisfaction, low cost, good tolerance and high reproducibility[10-13].

Two studies[14,15] compared other imaging methods with MBI to assess dense breasts. These studies selected Chinese women with dense breasts upon mammography and submitted them to other investigation methods, such as ultrasonography (US), magnetic resonance imaging (MRI) and MBI. In both studies, the sensitivity and specificity of each method were investigated. Yu et al.[15] concluded that the isolated sensitivity and specificity of MBI were, respectively, 80.35% and 83.19% for the detection of breast cancer. The MBI, however, has low sensitivity to detect axillary lymph nodes (32%). Zhang et al.[14] evaluated the sensitivity, specificity and diagnostic accuracy of the combination of mammography and MBI versus mammography and US. The increased diagnostic specificity of MBI was 30.8% versus 20.6% of US (10.3% difference, p = 0.003). There was no difference between MBI or US in increasing the sensitivity of diagnosis in mammography (increased sensitivity 25.2% versus 22.1%, difference 3.2%, p = 0.23).

The study by Rhodes et al.[6] showed the performance characteristics of MBI and mammography for screening cancer in women with dense breasts. Combined mammography and MBI were significantly more sensitive than mammography alone (91% versus 27%, p = 0.016). MBI and mammography specificities were similar (93% and 91%, respectively). The positive predictive value (PPV) of a screening test with abnormal results was significantly higher for MBI compared to mammography (12% versus 3%, p = 0.01). Although recall rates for mammography and MBI did not differ significantly, there was a trend towards a lower recall rate for MBI[16]. However, Hendrick and Tredennick reported that, while the lowest dose of MBI has benefit-risk estimates greater than 1 for women with dense breasts and age 40 years or older, this estimate is not outweighed by the benefit-risk related to screening mammography[17].

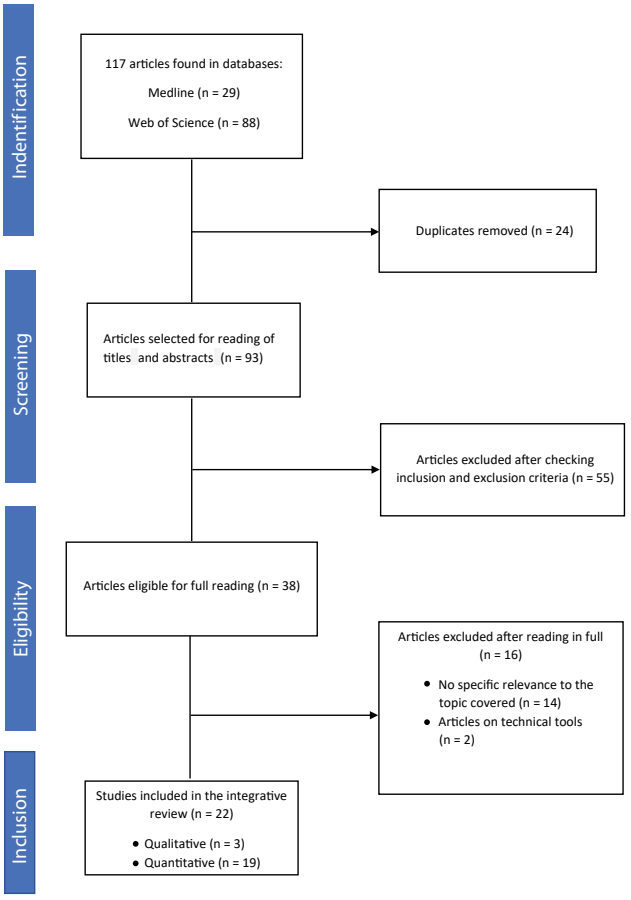

Figure 1. Article search and selection process.

Several techniques can be used to further screen women with dense breasts. Low radiation dose MBI can be one of these[18]. BPU of fibroglandular tissue, which refers to the level of Sestamibi-^{99m}Tc uptake within fibroglandular tissue on molecular breast imaging (MBI), has been identified as a strong risk factor for breast cancer, regardless of mammographic density[2,19,20].

Yoon et al. investigated factors that could affect MBI background uptake in normal breasts and the impact of MBI background uptake on the diagnostic performance of MBI. Background parenchyma enhancement (BPE) on MRI was the most important factor. A high background uptake or marked BPE can decrease the diagnostic performance of MBI[21].

Some studies used subjective categories to classify BPU into four groups: photopenic aspect (lower uptake than that observed in subcutaneous fat), minimal to mild (equal to or a little higher than fat), moderate (greater than mild, but less than twice the uptake in fat) and accentuated (at least twice greater than seen in fat)[2,3,19,22]. Due to possible variations between different observers, a quantitative method was proposed for a more accurate reproducibility of this classification[2].

A retrospective study carried out in 2015 with more than 1,100 women reported some clinical factors as associated with higher levels of BPU. Young, non-menopausal patients on hormone replacement therapy (HRT) were rated in the moderate to severe category[23]. Another study showed effects of menstrual cycle phase on BPU. When high BPU values were seen, they were more frequent in the luteal phase and in women with dense breasts[24]. Hruska et al. stated that short-term intervention with low-dose tamoxifen can reduce BPU in MBI for some patients. Preliminary findings suggested that tamoxifen at 10 mg per day was more effective than 5 mg to induce BPU decay in 30 days[20].

A study from 2018 with 153 women associated the MBI PPV in relation to the character of the lesions, BPU and breast density. Mass or non-mass variability in the character of lesions was not a good determinant of malignancy likelihood. Furthermore, it was concluded that BPU heterogeneity did not significantly affect the prediction of positivity. However, dense breasts had more findings than non-dense breasts[22].

The association of BPU with predicting the development of breast cancer in post- and pre-menopausal women in five years was evaluated in a 2020 cohort. Increased BPU was shown to be associated with an increased risk of breast cancer in post-menopausal women. However, a non-significant association was seen in premenopausal women. In postmenopausal women, BPU provides discriminatory accuracy to predict breast cancer risk when combined with the Gail or BCSC models (which include risk factors in the assessment). The group of postmenopausal women, with low BPU and on hormone replacement therapy was reported as having the lowest risk for breast cancer[3,25].

DISCUSSION

MBI in clinical practice, as a complement to mammography in the detection of breast cancer, has been reported by several studies[6,7,22]. The pros of this imaging method are: easy interpretation, high rate of inter-observer agreement, high diagnostic accuracy and not being operator-dependent, like ultrasonography. However, the method does have some disadvantages, including the use of radiation and low sensitivity in detecting axillary lymph nodes[15].

When compared to MRI, MBI has similar sensitivity and specificity for breast cancer, except in women who are at high risk of developing the disease, in which the sensitivity of MBI is slightly higher than that of MRI[7]. However, further studies are needed to better characterize this difference.

The cost of MBI is comparable to the cost of 3D mammography and approximately one-tenth of the cost of MRI[11]. The addition of MBI to screening mammography in women with dense breasts was already proven to increase the overall cost and rate of benign biopsies. However, there is an increase in cancer detection when compared to mammography alone, which represents a great advantage, as it results in a lower cost per case detected[18].

Although concerns about exposure to MBI radiation have limited its acceptance in the past, low doses have enabled the use of this method for routine screening[3]. This allowed an effective supplemental imaging technique for subgroups of women in which the sensitivity of mammography is limited. However, further studies are needed to assess whether MBI could replace mammography in certain populations or whether the two modalities could be used together[16].

MBI images are known to have high sensitivity in detecting breast cancer, both in patients with dense breast tissue and in patients with non-dense breast tissue. Choi et al. showed that the accuracy of predicting malignancy in breast lesions could be improved by analyzing uptake characteristics rather than diagnosing malignancy based solely on the presence of radiotracer uptake. The results also associate higher uptake intensity with a higher frequency of malignancy[8].

With regard to patients with dense breasts, studies suggest that MBI is a very useful imaging modality for the detection of tumors[12,13]. The increase in MBI as an adjuvant method can promote early detection of breast cancer, offer more treatment options and reduce morbidity and mortality among these patients[14,15]. Furthermore, considering the supplementary assessment of dense breasts through MBI, the recall rate to reassess the exam varies from 7% to 13%, which is lower than that reported for breast ultrasound and MRI[11].

BPU assessed in the MBI of women with dense breast tissue can function as an additional risk factor that can help identify the subgroup of patients that would most benefit from screening or primary prevention options[19]. BPU was shown to be strongly associated with the risk of developing breast cancer, regardless of mammographic density and hormonal factors[2].

However, a study by Hruska et al. showed higher BPU values during the luteal phase in non-menopausal women, compared to the follicular phase of the menstrual cycle, and in women with dense breasts compared to women with non-dense breasts[24]. Another study showed that postmenopausal women with dense breasts and high BPU were identified as being at particularly high absolute risk, while the lowest risk subgroup were postmenopausal women on hormone therapy with low BPU. This finding suggests that low BPU may identify a subset of women with hormone-unresponsive breast tissue and therefore no increased risk of breast cancer due to hormone therapy[3].

Short-term administration of low-dose tamoxifen has shown a reduction in BPU in some women, which could suggest that this medication reduces the risk of breast cancer. However, given the variability of BPU response to tamoxifen among the study participants, a future study is needed[20].

CONCLUSIONS

We can conclude, after a careful review of the studies selected, that the use of MBI as a complementary screening method for dense breasts would be of great value in clinical practice, as it can increase the diagnostic sensitivity and specificity at low cost and good tolerance by patients.

The use of BPU along with MBI should be considered in these patients, since the level of fibroglandular tissue uptake was associated with risk of developing breast cancer, regardless of mammographic density and hormonal factors, which allows for the identification of a subset of women with dense breasts upon mammography and at high risk of developing neoplasia.

AUTHORS' CONTRIBUTION

C.L.S.V.: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review & editing.

LPCVG: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration,

resources, software, validation, visualization, writing – original draft, writing – review & editing.
DNP: Data curation, formal analysis, funding acquisition, investigation, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review & editing.
ASM: Data curation, formal analysis, funding acquisition, investigation, resources, software, visualization, writing – original draft.
RFBA: Conceptualization, formal analysis, methodology, project administration, resources, supervision, validation, visualization, writing – review & editing.

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REVIEW ARTICLE
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Pseudoangiomatous stromal hyperplasia of the breast: a rare condition – from diagnosis to treatment

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ABSTRACT

Pseudoangiomatous Stromal Hyperplasia (PASH) of the breast is a rare condition that consists of the proliferation of the breast myofibroblastic stromal cells, lining anastomosing vascular slit-like spaces. This condition is not considered a pre-malignant lesion and affects mainly premenopausal women. Its etiology is still uncertain, but its behavior points to a hormonal cause. It has a varied clinical presentation and can be diagnosed as an incidental finding of biopsies or with the manifestation of clinical signs and symptoms. As for the diagnosis, it can be performed with the correlation between clinical data, imaging and histopathological analysis. Due to its rare nature, there are still no prospective studies regarding treatment, but, in most cases, clinical and radiological follow-up is a safe strategy. The aim of this paper is to synthesize the data available in the literature about this condition, which, although benign in nature, can bring important aesthetic, musculoskeletal and psychological repercussions.

KEYWORDS: breast diseases; angiomatosis; hyperplasia; diagnosis; signs and symptoms; therapeutics.

INTRODUCTION

Pseudoangiomatous hyperplasia of the breast stroma or pseudoangiomatous stromal hyperplasia (PASH) is a rare condition that consists of the benign proliferation of myofibroblasts in the breast stroma, forming anastomosing canaliculi similar to vascular clefts. It was first described in 1986, by Vuitch et al.[1], who classified the lesion as "mammary stromal proliferations that simulated vascular lesions." PASH is not related to malignant lesions or considered a premalignant lesion[2] and affects mainly pre-menopausal women[3,4]. Its etiology is still uncertain, but the main hypothesis is an aberrant hormonal stimulation and responsiveness as a cause[3,5]. PASH can be associated with other benign and malignant lesions of the breast. Its clinical presentation has a varied spectrum, being diagnosed incidentally after the histological analysis of biopsy samples performed to evaluate other lesions, as nodules or palpable masses and/or breast enlargement[5,6]. Sometimes we run into situations of difficult diagnosis and breast changes with intriguing behavior, leading us and our patients to great distress, subjecting them to aggressive and sometimes unnecessary interventions. The purpose of this review is to contribute to a better knowledge and understanding of PASH, improving the reasoning and the approach of our patients.

ETIOPATHOGENESIS

Although the etiology still remains uncertain, a widely accepted theory is that there may be a hormonal cause that generates PASH, based on several observations[7,8]. It is difficult to establish risk factors and/or the initiation of this lesion, as there is a strongly accepted hypothesis that neoplastic lesions that have a hormonal cause do not depend on a toxic or infectious specific agent to trigger its changes. In this case, for various reasons, there is an exacerbated reactivity to endogenous or exogenous hormonal stimuli, which provides mutations in the genetic material of cells sensitive to these hormones[9].

The histopathological and immunohistochemical analysis usually shows the expression of hormone receptors, especially progesterone, in myofibroblasts from PASH-positive samples. This is the first observation that leads to a hormonal cause[5]. Another fact that points to this etiology is the distribution of the prevalence of this breast lesion according to age: the lesion is often present in women in the pre and perimenopause period[3,4,10], and the clinical presentation in those who have already gone through menopause is usually minor injuries, or lesions associated with hormone replacement[5]. A case of lesion reduction with the use of tamoxifen also sheds light on the possibility of hormonal influence[11]. When PASH manifests itself in males, it is

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usually associated with gynecomastia[12]. Another characteristic that corroborates this hypothesis is the variation in the size of the lesion observed according to the menstrual cycle[13]. These facts all contribute to the thought that hormones, whether endogenous or not, act by stimulating the stromal cells of the breast, culminating in hypersecretion of extracellular matrix rich in collagen, characteristic findings of PASH[8].

In addition to the influence of progesterone on the genesis and evolution of PASH, another hormone was raised as a possible contributing factor in the process: prolactin. This peptide is a fundamental hormone to promote the proliferation and differentiation of the breast parenchyma and milk production. Some situations, such as hyperthyroidism, can cause an increase in circulating levels of this hormone, that is, a hyperprolactinemia. This condition leads to increased secretion by epithelial cells and expression of nuclear factor kappa B (NF-κB), which results in an inflammatory response in the cells of the breast epithelium. Therefore, there may be an association of prolactin levels with the development of PASH[8].

CLINICAL MANIFESTATIONS

PASH predominantly affects women in the pre or perimenopause, and those in the post-menopause, especially the ones under hormone replacement therapy[3,4,10]. It can also more rarely affect people of the male sex and individuals in childhood[14-16]. When comparing the clinical presentation among women in the post-menopausal phase with those who have not yet undergone this physiological event, the lesions are usually larger in women in pre and perimenopause[5].

PASH is a condition that has a wide spectrum of clinical presentations. It can manifest asymptomatically, with an incidental diagnosis when analyzing samples of biopsies that were performed to evaluate other lesions, whether benign or not. The prevalence of incidental diagnosis of PASH in these situations has been reported in studies, ranging from 6.4% to 23%[2,3].

The proportion of cases presenting as symptomatic and asymptomatic is variable between published studies. There are studies that report that the predominant form is symptomatic[13], while others report a predominance of diagnosis by means of an incidental finding on biopsy[8,17].

The proportion of male individuals who present gynecomastia and have findings suggesting PASH at biopsy ranges from 24% to 47%[18], as it highlights the need to consider PASH a differential diagnosis or an associated change in male individuals who complain of gynecomastia.

Among symptomatic individuals, PASH can manifest itself as a palpable nodule or localized mass[7], which can be clinically similar to fibroadenoma[17], or a rapid, diffuse and accentuated growth of unilateral or bilateral breasts (which can be symmetrical or asymmetrical)[6,14,19,20]. A case of presentation as an axillary nodule has also been reported[21]. Depending on the proportion of breast growth, this manifestation can have aesthetic and musculoskeletal repercussions that are the motivation for seeking medical care.

DIAGNOSIS

The diagnosis of PASH is based on a set of clinical, radiological and histopathological data. The clinic, as mentioned in the previous topic, has a variety of presentations.

Macroscopically, when PASH forms a palpable mass, it appears as a firm, well-defined, circumscribed and unencapsulated mass of 1 to 12 cm in size (Figure 1). The cut surface shows a light brown and homogeneous color; in some cases, the lesion may be multinodular (Figure 2). For the histopathological analysis, a sample of

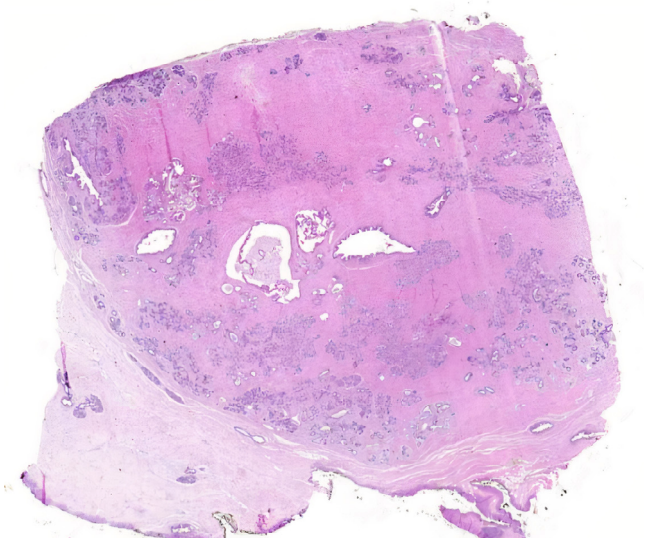

Figure 1. Pseudoangiomatous stromal hyperplasia of the breast forming a well-defined, non-encapsulated nodular mass, at a magnification of 0,5 times.

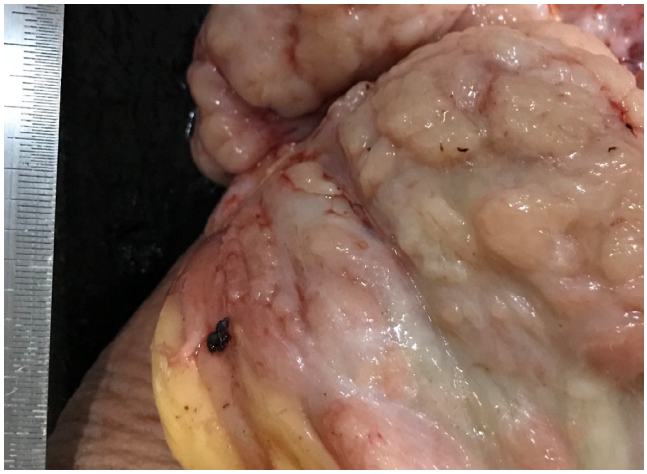

Figure 2. Macroscopic view of pseudoangiomatous stromal hyperplasia of the breast, in its multinodular form.

the lesion can be obtained by incisional, core or excisional biopsy. The typical finding is well described and generally sufficient for diagnosis. There is proliferation of collagenized, hyalinized and acellular connective tissue, filled with spaces in the form of anastomotic slit-like spaces, devoid of red blood cells and lined by flattened and fusiform stromal cells — myofibroblasts, like endothelial cells, simulating vascular channels. The presence of intermixed terminal duct lobular units is observed (Figure 3)[1,5]. Features that are commonly associated with malignancy, such as pleomorphism or nuclear atypias and mitosis figures, are generally not found in PASH[4,5].

PASH can be classified in two ways, according to the histological aspect of the lesion: the simple form and the fascicular or proliferative form. The simple type exhibits mainly anastomosing spaces, while the proliferative or fascicular type is characterized by areas of spindle cell proliferation, simulating myofibroblastoma[5].

Due to the similar microscopic or macroscopic characteristics of the lesion, PASH must be distinguished from low-grade angiosarcoma, other vascular tumors and phyllodes tumor[8,20]. What helps with this differentiation, in addition to the morphological benign characteristics, is the immunohistochemical staining for some myofibroblast markers. In PASH, stromal cells show positive staining for hormone receptors (progesterone more often, and estrogen to a lesser extent), actin, desmin, and for CD34. As for other markers, they are usually negative, such as cytokeratins, vimentin, calponin, S100, and endothelial markers, factor VIII and CD31. Immunohistochemical staining has also been reported in one study to be negative for the lymphatic endothelium marker, D2-40 or podoplanin[4,5,13].

Biopsy is indicated only when another lesion, other than PASH, is suspected in imaging analysis. Therefore, when there is agreement between clinical and imaging findings, in which both suggest a benign lesion, there is no need to perform this procedure. In turn, when indicated, the biopsy is sufficient to diagnose PASH. Alterations can be unifocal, multifocal or diffuse and can be found associated with other benign lesions, such as fibroadenoma and gynecomastia, pre-malignant or even malignant conditions, such as phyllodes tumor. If a hidden malignancy is suspected, surgical excision is recommended. Fine needle aspiration puncture has no specific findings and should not be performed for diagnosis[8].

IMAGING

In general, on imaging studies, the lesions present characteristics of benignity. Mammography, ultrasonography (especially in cases of inconclusive mammography and in people of an earlier age) and magnetic resonance imaging (which is not routinely used, but can help with lesion assessment and surgical planning) can be used as diagnostic tools[16].

At mammography, the most common findings are a non-calcified solitary nodule and localized stromal enlargement[22]. An irregular density can also be seen[10]. Therefore, PASH with a presentation of a single nodular lesion has the typical characteristics of a benign finding at mammography. Usually, in these cases, it can be classified as BI-RADS 2 or 3; in cases where it is a diffuse lesion, we can find a BI-RADS classification 4[13,23].

Ultrasound findings are a well-defined hypoechoic mass of varying shapes and may present posterior echogenic enhancement. However, this propaedeutic method can present itself without changes in normality[10,22].

The findings that are found in nuclear magnetic resonance are varied and usually non-specific. It can present an isointense image in relation to the normal T1 mammary parenchyma, in addition to hyperintense reticular and cystic areas. Regarding the pattern after contrast injection, an initial rapid enhancement has already been observed, followed by a slow and gradual delayed enhancement[24].

These imaging findings have nonspecific patterns and have an important role in assessing the extent of the lesion, evaluating suspicious characteristics of malignancy in order to indicate an extension of the investigation and, in the case of ultrasound, to be able to guide the biopsy. In addition, they are useful in medical follow-up, indicating signs of evolution of the lesion.

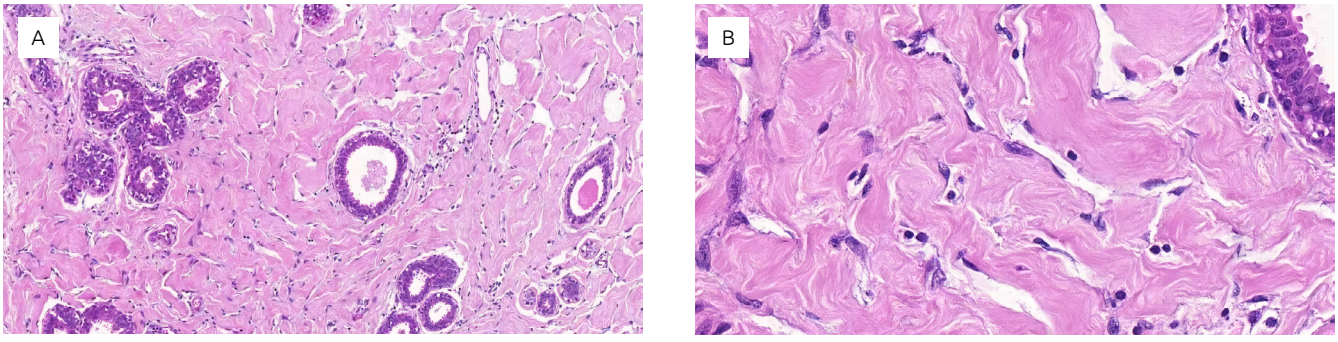

Figure 3. Pseudoangiomatous stromal hyperplasia of the breast: Dense and collagenized breast stroma with anastomosing channels lined by myoepithelial cells, simulating vascular channels. Presence of intertwined duct-lobular epithelial units. Hematoxylin and Eosin, at a magnification of 10 and 40 times.

THERAPEUTIC APPROACH

The American Society of Breast Surgeons does not recommend routine surgical excision of PASH when suspected on imaging or diagnosed in an incisional biopsy sample[25]. Clinical and radiological follow-up is a safe strategy. Surgical treatment can be performed in those cases in which there is genetic predisposition to cancer and important aesthetic deformities or repercussions. Surgical treatment can also be an option based on the patient's preference[8].

A surgical approach can be indicated at any time during the clinical-radiological follow-up, if any of the following conditions are found: progression of the lesion (that is, increase in the size of the lesion), inconclusive findings regarding histology and/or suspicious aspects of malignancy in radiological propedeutics[26]. PASH can be often considered a condition classified as BI-RADS 2 or 3, as mentioned above, and when it is incidentally diagnosed, it does not require any active management[13].

The initial approach is based on the clinical manifestations and the findings on imaging and pathological analysis. It should be clinical observation, vacuum-guided excision or surgical excision and, in some selected cases, unilateral or bilateral mastectomy. The choice of the surgical modality can be based on the size of the lesion, the patient's desire and the surgeon's experience[8,27,28].

Tamoxifen, despite having already been reported as a management strategy, is not recommended, due to its side effects and the contraindication for use in pre-menopausal women[13].

EVOLUTION

It is known that PASH is not considered a premalignant lesion[2]. Although there are reported cases of associated malignant lesions, sometimes in the same focus, there is not enough data to affirm that PASH is a precursor lesion, to the detriment of the hypothesis that it had just overridden the malignancy. However, there is an isolated case report in which an unequivocal evolution towards malignant lesion was observed[29]. Nevertheless, the database is not very extensive and there is no study capable of proving causality.

Most of the studies and published reviews have not demonstrated evolution to malignant lesions. They even demonstrate a lower proportion of malignant lesions in those patients who were diagnosed with PASH[2], without a proven relationship. One possible explanation, however, is that clinical-radiological follow-up of PASH allows for an early detection of possible malignancies that arise, but without having PASH as the cause.

The risk of progression (increase in the lesion that was primarily diagnosed as PASH, during clinical-radiological follow-up) may be influenced by the result of the biopsy of a fragment of the lesion (if there is any condition other than PASH), symptoms (palpable mass or accentuated increase in the breasts) and size (> 30 mm). The risk of recurrence or emergence of new outbreaks of PASH varies from 0.4% to 23%[8].

FINAL CONSIDERATIONS

PASH is a benign and rare condition of the breasts that was first described approximately 34 years ago, but which still does not have a consensus on its etiology, evolutionary behavior and ideal treatments, despite being increasingly standardized. Most published studies on this condition consist of case reports and case series, which limits decision making.

However, it is important that PASH be part of the collection of differential diagnoses for patients who seek care with any symptoms related to the breasts. In spite of its benign nature, it can cause uncomfortable symptoms, and the professional attending a case should individualize, based on clinical examination, complementary radiological study, histopathological analysis and the patient's desire, the best treatment and follow-up strategy.

AUTHORS' CONTRIBUTIONS

J.R.A.: Data curation, Formal analysis, Writing – original draft.
C.B.N.: Writing – review & editing.
C.E.M.L.: Conceptualization, Methodology, Supervision, Writing – review & editing.

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REVIEW ARTICLE
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Metaplastic breast carcinoma: series of cases and literature review

Giulia Papa[1], Carolina Fernanda Ferreira[1], Luisa Damasio[1], Karla Calaça Kabbach Prigenzi[1]*

ABSTRACT

Introduction: Metaplastic breast carcinoma is a heterogeneous group of infrequent invasive carcinomas with aggressive behavior. It presents differentiation from the neoplastic ductal epithelium to squamous and/or sarcomatous mesenchymal component, through the epithelial-mesenchymal transition process, and may present morphology of epithelioid and fusiform cells, with possible cartilage, bone, lipomatous, fibromatous, smooth muscle or skeletal muscle differentiation, among others. Most of the cases present the triple-negative immunohistochemical profile. **Objective:** To report three cases of metaplastic carcinomas, with an emphasis on clinical and pathological aspects, in addition to conducting a literature review on this topic. **Methods:** The three cases were registered in the internal search system for reference services in breast pathology in São Paulo, between 2012 and 2019. For literature review, the keywords *metaplastic carcinoma, breast, cancer, review, breast cancer subtype* and *pathological and clinical outcomes* were used in PubMed. We found 154 articles, of which 42 were selected for full reading, based on the abstract and established inclusion criteria. After this initial selection, these articles were read and reviewed; nine articles that did not meet the inclusion criteria were excluded. **Discussion:** Three cases of metaplastic carcinoma with similar immunohistochemical characteristics have been reported. The first case is that of a 40-year-old patient with the diagnosis of metaplastic carcinoma producing a chondroid matrix with liposarcomatous and osteosarcomatous differentiation. The second case is that of a 50-year-old patient who presented with the final diagnosis for a fusocellular metaplastic carcinoma with lymph node metastasis. Finally, the third case described is that of a 59-year-old patient, who presented metaplastic carcinoma with chondroid differentiation. **Conclusion:** Metaplastic carcinoma is a rare and aggressive type of breast cancer, in which most of the patients have shorter survival and worse prognosis in relation to the other subtypes. More studies are needed in order to determine a gold standard treatment for this disease.

KEYWORDS: triple negative breast neoplasms; breast; neoplasms; review; neoplasms by histological type; treatment outcome.

INTRODUCTION

Metaplastic breast carcinoma is a heterogeneous group of rare invasive carcinomas with an aggressive profile, which represent approximately 0.2%–1% of malignant breast tumors[1]. This tumor is characterized by the differentiation of the neoplastic ductal epithelium into squamous and/or sarcomatous mesenchymal components, and may present a varied cellular morphology of epithelioid and spindle cell patterns or with specific differentiation for some mesenchymal lineage[2,3]. Its clinical presentation is similar to that of invasive breast carcinomas of no special type (NST), the former invasive ductal carcinoma, and to benign breast lesions, which makes its radiological diagnosis challenging. Metaplastic carcinomas present at diagnosis in more advanced stages. Association with microcalcifications is not common in this type of tumor, except for cases with ductal carcinoma in situ and/or bone differentiation. Several studies indicate that metaplastic breast carcinoma is negative for estrogen receptor (ER), progesterone receptor (RP), and human epidermal growth factor — receptor 2 (HER2) on immunohistochemical examination, which leads to a common generalization of these tumors as triple-negative breast cancer. However, its clinical behavior is different from other tumors included in this same group[1,4]. Thus, even though most metaplastic breast carcinomas have a triple-negative phenotype, as do some NST, the clinical outcomes of both are different, with metaplastic carcinomas mostly having a worse prognosis[1,4]. Furthermore, when comparing the two types of tumors, metaplastic breast carcinoma metastases occur in more distant locations, such as the brain and lung, with a lower incidence of regional lymph node metastasis[5].

Clinically, most cases manifest as a palpable nodule, and the characterization of the lesion may be possible both by ultrasound and mammography[1,6]. Macroscopically, they may appear as

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well-circumscribed or indistinct-appearing masses with irregular edges. Nielsen et al. suggest that metaplastic breast carcinoma may appear as benign circumscribed, round, or oval masses on mammography; lobular, circumscribed and solid with posterior echogenicity on ultrasound; or even with T2 hyperintensity on magnetic resonance images[7].

OBJECTIVES

The main objective of this work was to report three cases of metaplastic carcinomas, with emphasis on clinical and pathological aspects. As a secondary objective, we propose to review the literature on this topic.

METHODS

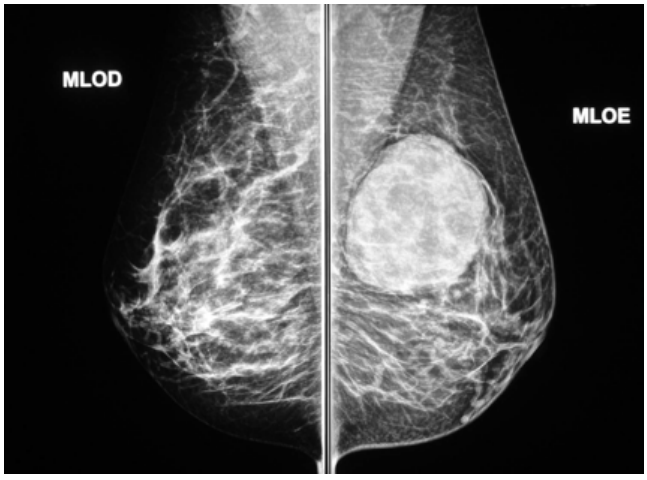
A retrospective search of cases with a diagnosis of metaplastic breast carcinoma was carried out, in an internal search system of a reference service in breast pathology in São Paulo, between 2012 and 2019. For this search, we selected, in the field of biological material, only surgical resections of breast, and, in the diagnostic field, the term metaplastic carcinoma of the breast. Three cases were found with such a diagnosis, which are detailed below. As this is a case report study, the research is exempt from the free and informed consent, as only data collection was carried out from medical records and reports of imaging and pathological examinations, not involving any intervention in patients.

To review the literature, the keywords *metaplastic carcinoma, breast, cancer, review, breast cancer subtype*, and *pathological and clinical outcomes* were used to search in PubMed. A total of 154 articles were found, of which 42 were selected for full reading based on the abstract and inclusion criteria. Articles in English were included, which were case reports referring to the diagnosis under study or those that performed a literature review or systematic review on the topic, including demographic, imaging, anatomopathological, immunohistochemical, molecular, and differential diagnosis data. After this initial selection, this literature was read and reviewed, and nine articles that did not meet the inclusion criteria were excluded (five described with greater emphasis another histological subtype of breast cancer, two were in Mandarin, and two in French), totaling 33 reviewed articles. Books from the World Health Organization (WHO) and national data from the National Cancer Institute (*Instituto Nacional de Câncer* — INCA) were also used as bibliographical references and supporting literature.

CASE REPORT

Case 1

A 40-year-old female patient presented with a rapidly growing nodule in her left breast for five months. Mammography showed a nodule at the intersection of the left upper quadrants, measuring 7.5 cm, with irregular contours and partially defined limits, classified as BI-RADS 4 (Figure 1). Ultrasound showed a hypoechoic nodule, with lobulated contours, measuring 4.8 x 3.2 x 0.6 cm (Figure 2). Core needle biopsy was performed, with a diagnosis of malignant epithelial-myoepithelial neoplasia. The patient underwent total mastectomy. Macroscopically, a nodule with well-defined borders, lobulated contours and firm consistency was observed. Histological sections showed poorly differentiated malignant neoplasm, forming solid blocks composed of epithelioid cells, with vesicular nuclei, little evident nucleoli and numerous atypical mitotic figures (Figure 3). It was also observed basophilic chondroid matrix and foci of background osteoid matrix. There were foci with lipoblasts



MLOD: right nipple; MLOE: left nipple.

Figure 1. Case 1: mammography shows a nodule at the intersection of the upper left quadrants, with irregular outlines, partially defined limits, BI-RADS 4.

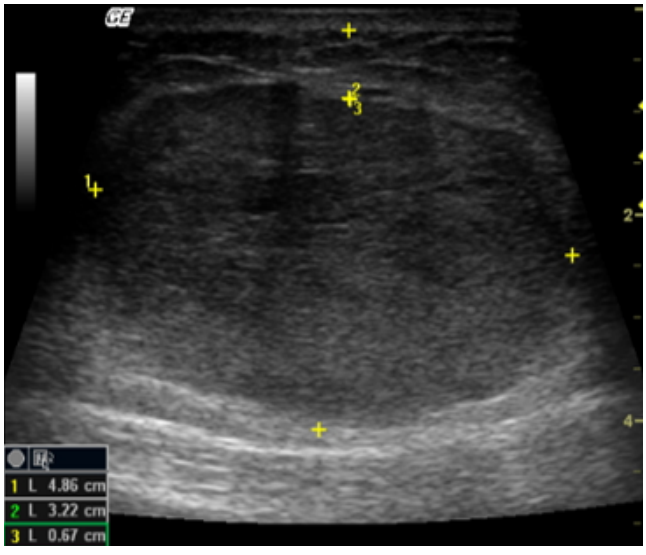


Figure 2. Case 1: ultrasonography shows a circumscribed, oval nodule, parallel to the skin.

and osteoclast-like multinucleated giant cells. The immunohistochemical study showed a triple-negative profile associated with immunoexpression of cytokeratin 7 (CK 7), p63, S100, EGFR, cytokeratin 5/6 (CK 5/6), vimentin and high cell proliferation index evaluated by Ki67, being the immunomorphological aspects compatible with the diagnosis of metaplastic carcinoma producing chondroid matrix, with liposarcomatous and osteosarcomatous differentiation. Axillary dissection was also performed, and no lymph node metastases were detected.

Case 2

A 50-year-old female patient presented with a well-delimited nodule in the right breast, classified according to the mammography as BI-RADS 5. A core needle biopsy was performed, with a diagnosis of malignant spindle cell neoplasm, suggestive of sarcoma. The patient then underwent a total mastectomy. Macroscopically, there was a 3.9 cm nodule, well delimited. Microscopically, malignant neoplastic proliferation was evidenced, predominantly composed of spindle-shaped cells, arranged in elongated, sometimes intersecting, bundles, in addition to a smaller component of epithelioid cells. Nuclei had vesicular loose chromatin, faint nucleoli, and numerous mitotic figures (Figure 4). The immunohistochemical examination revealed negativity for hormone receptors and HER2, with a high rate of cell proliferation at Ki-67, in addition to positivity for pancytokeratin (AE1/AE3), cytokeratin 7 (CK7), cytokeratin 5/6 (CK 5/6), cytokeratin 14 (CK14), smooth muscle actin, vimetin, S100, 34BE12, and EGFR, which concluded that it was a malignant neoplasm with epithelial and mesenchymal differentiation, compatible with the diagnosis of metaplastic breast carcinoma of the fusocellular type. Biopsy of the axillary sentinel and parasentinel lymph nodes showed the presence of macrometastasis in two of the three identified lymph nodes, with the largest focus measuring 15 mm.

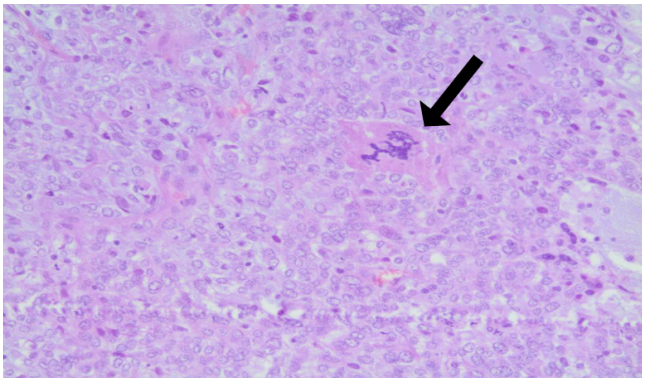


Figure 3. Histopathology of Case 1 (400x magnification): poorly differentiated neoplasm with formation of solid blocks composed of epithelioid cells, with little evident vesicular nuclei and nucleoli. Note the basophilic matrix in the background and an atypical mitosis figure (arrow).

Case 3

The third case is that of a 59-year-old woman, who presented with a rapidly growing mass in the left breast, measuring 8.7 cm in the longest axis, classified as BI-RADS 4. The histopathological analysis showed a solid neoplasm composed of epithelioid and rounded cells immersed in a myxochondroid-type stroma (Figure 5). Immunohistochemistry revealed a triple-negative profile, with positivity for CK 5/6, S100 and vimentin, compatible with metaplastic carcinoma with chondroid differentiation. Left axillary sentinel lymph node biopsy did not reveal the presence of lymph node metastasis.

DISCUSSION

Breast cancer is the most common malignant neoplasm among Western women. In Brazil, the incidence of this neoplasm was expected to reach 66,280 new cases in the year 2020[8], which

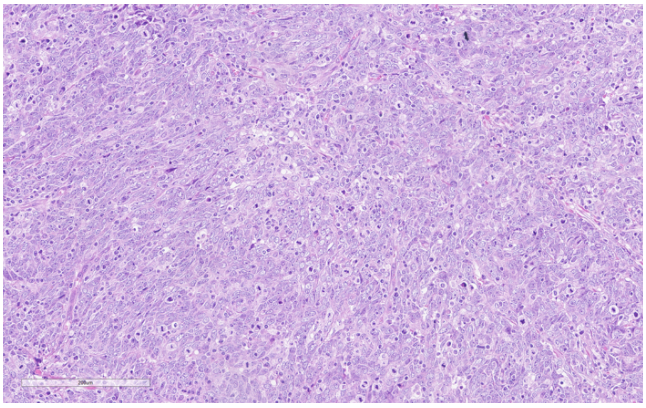


Figure 4. Histopathology of Case 2: neoplastic proliferation composed of spindle cells, arranged in elongated and sometimes intersecting bundles. Presence of vesicular nuclei with little evident nucleoli and numerous mitotic figures.

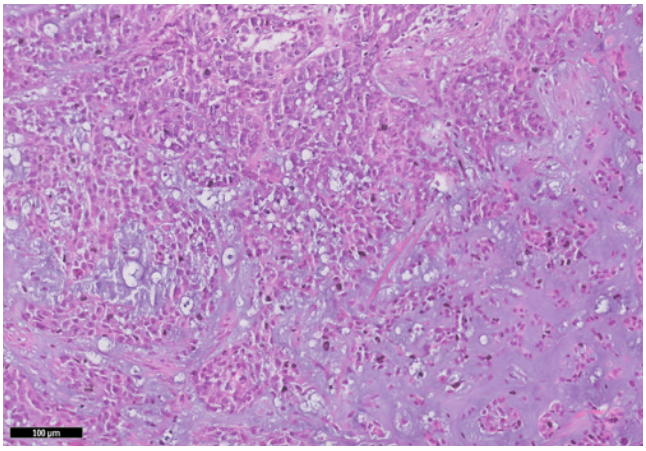


Figure 5. Histopathology of Case 3: solid neoplasm composed of epithelioid and round cells immersed in a myxochondroid-type stroma. Cells have little evident vesicular nuclei and nucleoli.

represents 29.7% of the total number of cancer cases in women. In this sense, breast cancer is considered the main cause of female death by cancer in the country, with the exception of non-melanoma skin tumors[9]. The most common histological invasive type of breast cancer is the carcinoma of no special type, formerly known as invasive ductal carcinoma (IDC) (70%–80% of cases), followed by invasive lobular carcinoma (ILC) (5%–15% of cases), and then by other histological types (medullary carcinoma, papillary carcinoma, metaplastic carcinoma, sarcomas)[8].

As for the gene expression evaluated by the immunohistochemical study of the ER, PR, and HER2 markers, four cancer subtypes are defined: luminal A (ER+ and/or PR+, HER2 negative and Ki-67 < 14%); luminal B (ER+ and/or PR+, positive HER2 and Ki-67 ≥ 14%); triple-negative or basal (ER-, PR-, HER2 negative) and overexpressed HER2 (ER-, PR-, HER2 positive). The most prevalent subtype described in the literature is luminal A, followed, respectively, by triple-negative, luminal B, and finally, overexpressed HER2[10]. Within the triple-negative group is the basal-like (basaloid) subtype, which expresses basal cytokeratins, such as CK 5/6. Basal-like breast carcinoma shows a more reserved prognostic pattern and several studies have associated it with lower disease-free survival and lower overall survival, when compared to other subtypes[6,7,11-13]. This subtype often presents complex genomic rearrangements and TP53 mutation[14-16], and has a strong association with mutations in the breast cancer gene 1 (BRCA1)[7,17]. Morphologically, this subtype is characterized by high histological grade, high mitotic index, presence of areas of central necrosis and prominent inflammatory infiltrate[12,13]. Studies show the presence of high nuclear grade, preponderance of tumor size between 2 and 5 cm and invasive ductal carcinoma as the most common histological type[18].

The first case reported here was 4.8 cm in size and, microscopically, it was a metaplastic carcinoma with epithelioid cells, vesicular pleomorphic nuclei and presence of basophilic matrix in the background, numerous atypical mitosis figures and triple negative immunohistochemical profile, with expression of CK 5/6.

The second case reported is a metaplastic spindle cell carcinoma, which is a very rare neoplasm and represents only 0.1% of all breast cancers[19]. This is a more aggressive variant of metaplastic carcinoma, characterized by highly atypical spindle cells, with areas of necrosis and evident mitotic figures[20]. According to studies by Khan et al.[20], metaplastic spindle cell carcinoma is clinically more common in postmenopausal women, manifesting in patients with a mean age of 55 years and presenting with a large and palpable mass (greater than T3 in 50 % of cases), presenting as an oval-shaped mass, with circumscribed margins and a slightly high density, classified as BI-RADS 4 or BI-RADS 5. In the case reported, the patient was 50 years old, has a tumor of 3.9 cm, staged as T2 and with BI-RADS 5 mammographic classification.

Microscopic examination of this type of tumor reveals an infiltrative proliferation of spindle cells with atypia and mitosis, which usually shows epithelial differentiation on immunohistochemical study, exemplified by the expression of CKs[21,22]. The histological pattern of the second case shows neoplastic proliferation composed of spindle cells, arranged in elongated bundles, which sometimes intersect, and with numerous mitotic figures. The differential diagnosis of metaplastic spindle cell carcinoma can be a malignant phylloid tumor and primary breast sarcomas. Phylloid tumors are negative for p63 and high molecular weight CK, whereas fusiform metaplastic carcinoma tends to be positive for both[23]. On the other hand, primary breast sarcomas do not show a morphological epithelial component or expression of CKs on immunohistochemical examination[23].

Immunohistochemistry is the key test that allows for a more accurate diagnosis. Fusiform metaplastic carcinoma is typically a triple-negative tumor, according to studies by Moten et al.[24], in which 286 cases are evaluated (from 1992 to 2011), with only 15% being positive for ER, showing the preponderance of triple-negative tumors. There are specific markers with high sensitivity and specificity for spindle cells, which are useful for diagnosis. Focal positivity findings for cytokeratin (AE1/AE3, CK 5/6, CK 7, and CK 14) and the presence of the S100 protein favor this type of neoplasia. There may be a positive reaction to muscle markers such as calponin and smooth muscle actin (SMA)[25,26], with p63 being a sensitive and relatively specific marker for epithelial cells[27,28]. In the case described, the patient was positive for AE1/AE3, CK 14, CK 7, S100, and AML and negative for CK 5/6, p63 and for ER, PR, and HER2 (triple negative).

The third case reported is a metaplastic carcinoma with chondroid differentiation, measuring 8.7 cm, classified as BI-RADS 4. Metaplastic breast carcinoma (MBC), as already mentioned, is an uncommon type of invasive breast carcinoma, and the chondroid differentiation is even more rare. Chondroid metaplastic carcinoma is known as matrix-producing carcinoma. Epithelial cells show a triple negative pattern and exhibit a high rate of cell proliferation (Ki-67), as reported in the case series by Gwin et al.[18] and other similar studies[29-31]. Chondroid cells exhibit a positive reaction for pancytokeratin (AE1/AE3) and S100, and a negative reaction for epithelial membrane antigen (EMA). Studies by Kim et al.[32] reported p53 overexpression in approximately 20% to 40% of conventional breast carcinoma cells and p53 overexpression in more than 60% of epithelial and chondroid cells in metaplastic breast carcinoma[32]. Metaplastic breast carcinomas with chondroid differentiation have a better prognosis than other subtypes[6]. In the case described here, immunohistochemistry revealed that it was a triple-negative tumor (RE, RP, and HER2), with positivity for CK 5/6, Ki67, S100, and vimentin.

The three cases reported presented nodules between 3.9 and 8.7 cm — the range of metaplastic breast carcinomas is usually 2 to more than 10 cm — and showed a histological pattern of cells with little evident vesicular nuclei and nucleoli. The BI-RADS classification of the presented mammograms were 4 and 5, being indicative of high risk for cancer. Regarding the immunohistochemical profile, there were similarities between the three cases described, with absence of expression of hormone receptors and HER2, configuring a triple-negative subtype (typical of metaplastic breast carcinomas). In addition, there was positivity for EGFR, vimentin, CK 5/6, and p63 associated with a high cell proliferation index (Ki-67) (Figure 6).

According to the analysis of the articles selected for review, it is possible to observe that most of these tumors have a shorter survival and a worse prognosis compared to the other subtypes, and their main therapy of choice is total mastectomy, axillary approach, adjuvant chemotherapy, and radiotherapy (Table 1)[3-5,20,23,28-30], treatments that were performed on the patients in question. However, as it is a rare and aggressive breast carcinoma subtype, two of the patients died, and another is disease-free, with a 2-year follow-up.

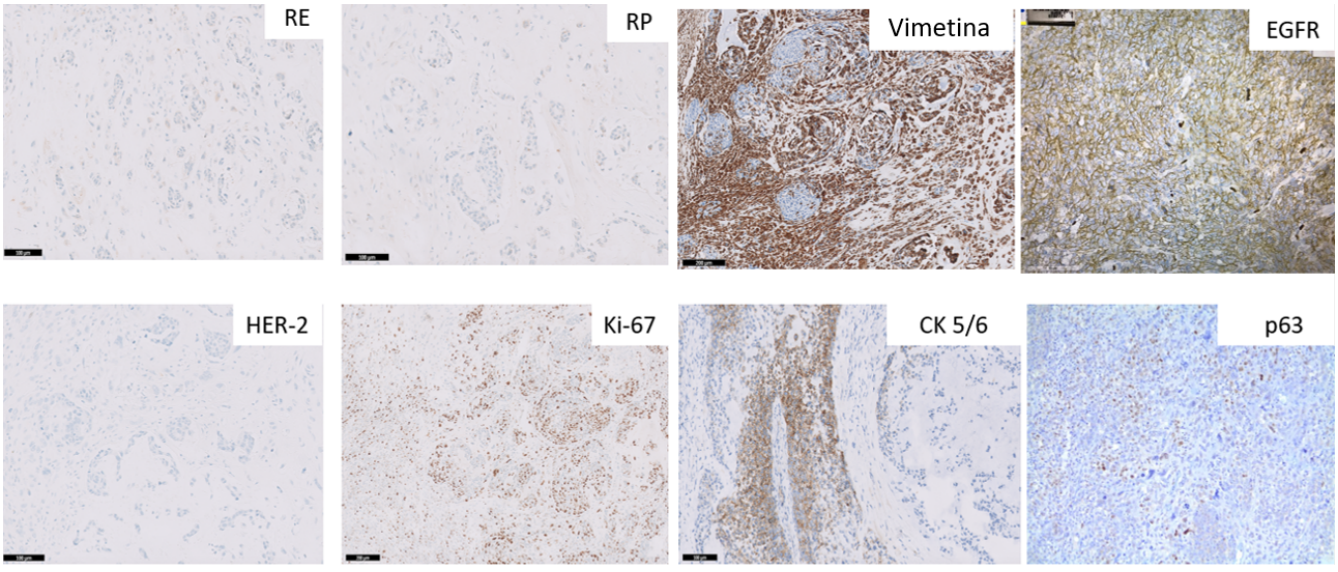


Figure 6. Immunohistochemical profile of reported cases: immunohistochemistry tests were positive for vimetine, EGFR, Ki-67, CK 5/6 and p63 and negative for ER, RP and HER-2 (triple negative).

Table 1. Summary of relevant data from the reviewed works regarding radiological findings, adopted treatment, and prognostic data.

Studies	Year of publication	Sample (N)	Design	Outcome
Han et al.[3]	2019	97	Case study	Matrix-producing tumors achieve better response to chemotherapy. However, this is not indicative of a survival advantage. **MBC prognosis and predictive factors:** further studies are needed.
El Zein et al.[4]	2017	554	Systematic review and Literature review.	**Survival:** MBC had fewer fully cured and overall survivors when compared to patients with TNBC. **Prognosis:** MBC has worse long-term clinical outcomes. **Treatment:** patients with MBC tended to receive mastectomy and chemotherapy more frequently than those with TNBC, while the latter received more radiotherapy. This difference in treatment may be a direct product of the MBC being at a higher stage compared to the TNBC.
McKinnon and Xiao[5]	2015	(-)	Literature review	**MMG:** MBC can mimic IDC and benign lesions. **Treatment:** depends on the size and number of axillary lymph nodes. There is evidence that associated radiotherapy promotes benefits.

Continue...

Table 1. Continuation.

Studies	Year of publication	Sample (N)	Design	Outcome
Khan et al.[20]	2003	19	Case series	**SC x-ray:** large mass is the only suggestive finding. **Average tumor size:** 53 mm. All tumors were ER and PR negative, limiting therapeutic options. **Nottingham Prognostic Index:** 5.2 **Primary treatment:** surgery (89%) — total mastectomy and partial mastectomy. **Survival:** 3.2% mortality, with an average of 18 months.
Chu et al.[23]	2014	117	Cohort	**Prognosis:** Triple negative and HER2 positive MBC have a worse clinical outcome. **Treatment:** - There was no difference between surgical treatment, adjuvant chemotherapy, hormonal therapy, and adjuvant radiotherapy. - The percentage of adjuvant radiotherapy in triple negative was higher than in HER2 and luminal due to the larger tumor size, positive lymph nodes and the possibility of later conservative therapy.
Moten et al.[24]	2016	286	Systematic review	**Treatment for spindle cell carcinoma:** - Partial mastectomy (38%). - Total mastectomy (55.5%). - Radiotherapy in 1/3 of patients. **10-year survival:** - Stages I and II: . Partial mastectomy: 83.9%. . Partial mastectomy + radiotherapy: 86.7%. . Total mastectomy: 71.6%. **Three-Year Survival:** -Stages III and IV: . Total mastectomy: 40%. . Total mastectomy + radiotherapy: 0%.
Cho et al.[25]	2014	1	Case report and literature review	SCC: **Radiographic characteristics:** oval mass with circumscribed and slightly hyperdense margins, BI-RADS 4 or 5. Microcalcifications on mammography are uncommon. **Prognosis:** uncertain — most important factors: size and grade. - Presence of p53 and p63 is associated with potentially high risk of malignancy and worse prognosis. **Five-year survival:** 28–68%. **Treatment:** limited, as they are typically triple-negative. There is no specific treatment established.
Zhu et al.[28]	2017	19	Systematic review	- Axillary lymph node metastasis in spindle cell MBC was less frequent than in IDC, as well as the expression of ER, PR, and HER2. **Treatment:** - It was noted that axillary dissection should not be done for breast sarcomas and sarcomas smaller than 5 cm required chemotherapy. - The surgery of resection of several foci together with postoperative radiotherapy proved to be more favorable for MBC of spindle cells of medium and high degree of differentiation, when compared to the conventional treatment.
Song et al.[29]	2013	55 + 767	Systematic review	**Prognosis:** - MBC has a worse prognosis than IDC and TN-IDC. - Factors with worse prognosis of MBC: tumor > 5 cm, presence of lymph nodes and Ki-67 ³ 14%. **Five-year survival rate:** - MBC: 54.5%. - IDC: 85.1%. - TN-IDC: 73.3%. **Five-year disease-free survival rate:** - MBC: 45.5%. - IDC: 71.2%. - TN-IDC: 60.3%.

Continue...

Table 1. Continuation.

Studies	Year of publication	Sample (N)	Design	Outcome
Schwartz et al.[30]	2013	(-)	Literature review	**MBC radiographic characteristics:** - Mammography: high density, circumscribed/obscure/ irregular and/or spiculated margins. Generally without calcifications. Round or oval shapes with circumscribed margins have a more benign appearance. - Ultrasonography: heterogeneous or hyperechoic solid or mixed mass. **Treatment:** - Response to chemotherapy in MBC (16.7%) is lower than in IDC (21–75%). - Neoadjuvant chemotherapy: minimally effective for MBC, with tumor shrinkage and progression prevention. **Prognosis:** worse overall prognosis compared to other standard invasive breast cancers.

MBC: metaplastic breast carcinoma; TNBC: triple negative breast cancer; SC: spinocellular carcinoma; IDC: invasive ductal carcinoma; SCC: squamous cell carcinoma; TN-IDC: triple negative invasive ductal carcinoma; Nottingham Prognostic Index: used to determine prognosis after breast cancer surgery. It uses three criteria: tumor size, number of lymph nodes involved, and tumor grade; HER2: human epidermal growth factor - receptor 2.

CONCLUSION

Three cases have been described as an extremely rare and aggressive type of tumor, usually classified radiologically as BI-RADS 4 and 5. Immunohistochemistry is an essential test for an accurate diagnosis of metaplastic breast carcinoma, and the three cases reported present triple-negative phenotype, which is a typical feature of this tumor. This exam is also able to differentiate similar tumors and identify the predominant cell type, which directly influences prognosis and treatment. Prognosis is related to staging, size, distant and lymph node metastasis, and most of these tumors have shorter survival and worse prognosis compared to other subtypes. Most of them have mastectomy as the treatment of choice, with an axillary approach, adjuvant chemotherapy and radiotherapy. However, due to the rarity of this histological type, there are insufficient data and guidelines for optimal treatment, and information about therapy is based on small retrospective studies rather than randomized studies. In this sense, further studies will be needed to determine a gold standard and personalized therapy for this disease.

AUTHORS' CONTRIBUTIONS

G.P.: Investigation, Methodology, Writing – original draft.
C.F.F.: Investigation, Methodology, Writing – original draft.
L.D.: Investigation, Methodology, Writing – original draft.
K.C.K.P.: Conceptualization, Data curation, Formal analysis, Project administration, Supervision, Writing – review & editing.

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REVIEW ARTICLE
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Hereditary breast cancer – what we have learned in the last decade

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ABSTRACT

This literature review aims to inform and assist physicians and other health professionals in managing all information related to hereditary breast cancer, which is in constant and rapid growth, allowing for improvement in patient care and assistance. In addition, we seek to better identify which patients are eligible for the clinical criteria of association with risk of hereditary breast cancer, based on international recommendations and highlighting the main high and moderate penetrance genes that make up the multigenic panels for germline investigation in breast cancer, as well as the possibilities of clinical management that must be considered when complex decisions are required in clinical practice. Nowadays, there is more interest in population screening, in a greater supply of genetic tests, more genes included in multigene panels — allowing the search for genetic counseling —, apart from the need for clinical-decision support.

KEYWORDS: hereditary breast and ovarian cancer syndrome; screening; genetic counseling; genetic testing; treatments; risk reduction.

LITERATURE REVIEW

Breast cancer and hereditary predisposition

Breast cancer is the most common malignant neoplasm whose mortality rates are the highest among the females worldwide. In Brazil, 66,280 new cases were estimated per year for the triennium 2020–2022 (43.74 cases per 100,000 women)[1,2]. Although there are several risk factors, breast cancer is associated with environmental, reproductive, genetic and lifestyle factors; family history is considered an important etiological factor[3].

The hereditary factor is a cause identified in 10–15% of breast cancer cases, and is associated with the Hereditary Breast and Ovarian Cancer Syndrome (HBOC), Li-Fraumeni Syndrome, Cowden syndrome, Peutz-Jeghers syndrome and hereditary diffuse gastric cancer in which lobular breast carcinoma may manifest in women[4–6].

The hereditary predisposition is most commonly seen in individuals and families with some clinical features such as: diagnosis of breast cancer in patients ≤45 years of age; breast cancer in men; personal and family history of ovarian, pancreas, bowel, endometrial, and prostate cancers at a younger age; and Ashkenazi Jewish origin[7].

Pathogenic variants

HBOC is mainly related to pathogenic variants in the *BRCA1* and *BRCA2* genes, which consist of germline mutations and account for almost 30% of all cases of hereditary breast cancer[8,9]. Other genes also have pathogenic variants associated with increased risk for hereditary breast cancer, such as *TP53, CHEK2, ATM, STK11, PALB2, PTEN*, among others, which demonstrates the complex genetic involvement when it comes to predisposition to this disease[10].

Over a lifetime, the presence of a pathogenic variant in *BRCA1* or *BRCA2* can increase the risk of breast cancer by up to 85%. For ovarian cancer, estimates reach 46% when the *BRCA1* gene is involved and 20% when the *BRCA2* gene is involved[4,11,12].

The *BRCA1* and *BRCA2* genes, identified in the 1990s, are involved in the activation of DNA repair in response to cellular stress, playing crucial roles in chromatin remodeling, transcriptional control and cell cycle regulation, with tumor suppressor effects primarily attributed to cell cycle checkpoints and DNA repair[13-15]. Some mutations are more common in individuals from specific ethnic or geographic groups. This is due to the presence of initiating mutations which probably arose several generations ago in

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this population. In Ashkenazi Jews (descendants of Central and Eastern Europe), three specific initiating mutations were identified: 185delAG and 5382insC in the *BRCA1* gene, and 6174delT in the *BRCA2* gene, and the same family group may have all three mutations. These variants are present in 2% of individuals in this group of women and are responsible for approximately 50% of early-onset breast cancer cases[16].

Another founder mutation identified in Portuguese Caucasian families with cases of breast cancer is the insertion Aluc.156_157insALU in exon 3 of the *BRCA2* gene, which promotes DNA rearrangements, altering the nucleotide sequence. The Brazilian ethnic composition also makes room for founder mutations in our population[17-19].

Another tumor suppressor gene called *TP53*, associated with the Li-Fraumeni syndrome, leads to increased risk for multiple tumors, including osteosarcoma, bowel cancer, adrenocortical carcinoma, leukemia, lymphoma, and brain cancer in addition to breast cancer[20]. This syndrome has an interesting peculiarity in patients diagnosed in the South and Southeast regions of Brazil: the founder mutation p.R337H has a prevalence of 0.3% due to the founder effect related to the movement of drovers in Brazilian territory[21].

The *PTEN* gene, responsible for cell cycle control, is associated with the Cowden syndrome and usually causes malignant tumors in the thyroid, breast and endometrium. Women with this syndrome have 25% to 50% risk of developing breast cancer, while the risk of endometrial carcinoma can reach 10%[5].

Pathogenic variants involving the *STK11* gene are associated with the Peutz-Jeghers syndrome, which increases the lifetime risk of breast cancer in women by up to 50%[5]. Furthermore, genes involved in the pathways of DNA double-strand break (DSB) such as *CHEK2, RAD51, BRIP1* and *PALB2*, may also be associated with hereditary cancer predisposition[22].

Most cases of breast cancers are invasive and the prognosis depends on the stage of the disease at the time of diagnosis[23]. In general, in developing countries, diagnoses occur at advanced stages, which is mainly due to the deficiency in promoting early detection[24]. In non-menopausal women, breast cancer represents a biologically more aggressive disease, with frequent adverse histopathological features and worse prognosis when compared to women over 50 years of age[25].

Hereditary breast cancer with *BRCA1* mutation often results in triple-negative breast cancers — approximately 80% of *BRCA1* mutation cases[24,26,27]. Histological characterization of tumors with *BRCA1* germline mutations suggests high histological grade, atypical medullary features, high proliferation rates, inflammatory infiltrates, and invasive borders. On the other hand, *BRCA2* mutation are related to tumors with a higher risk of contralateral breast cancer and estrogen receptor positivity in most cases[24,28].

Screening for hereditary breast cancer

Although physical examination is important to establish doctor-patient relationships and to evaluate symptomatic patients, it plays a less important role in breast cancer screening when compared to imaging methods such as mammography, magnetic resonance imaging (MRI) and ultrasonography, since it has low sensitivity in detect the disease and is thus insufficient to rule it out. In patients at increased risk, the sensitivity of the physical examination is even lower. However, it continues to be recommended once or twice a year for women aged 20–25 years of age and carrying pathogenic variants in *BRCA1, BRCA2, TP53* or *PTEN*[29].

For women in the breast cancer predisposition group, early mammographic screening is adopted, considering the earlier development of the disease, with the incorporation of complementary imaging tests such as MRI and ultrasound due to the limitations of the mammography examination for age groups below 40 years in the female population[30-32].

In the general population, mammography has shown to be related to a reduction in mortality rates, although its usefulness is less understood in women with pathogenic variants in *BRCA1, BRCA2, TP53, PTEN* and *STK11*, or with history of chest irradiation in the age of 10 to 30 years. In this group, annual mammography is recommended starting from 30 years old, with adjuvant MRI[10,29].

The guidelines related to the presence of pathogenic variants of moderate penetrance are less well-defined: annual mammography is recommended from the age of 40 onwards for patients with variants in *ATM, CHEK2* and *NBN*; and from the age of 30 onwards for cases of variants in *PALB2, CDH1* and *NF1*[10,29].

Although mammography remains an appropriate tool to screen the general population, its use alone may be insufficient to detect patients at increased risk of developing breast cancer. The method has less sensitivity in denser breasts, commonly present in younger patients, who constitute one of the groups considered at increased risk for hereditary breast cancer[29].

The MRI has a higher sensitivity compared to mammography to diagnose breast cancer in patients with hereditary predisposition. It is recommended annually from 25 to 30 years of age onwards in this group of women, also being considered annually from 30 to 50 years of age onwards — the age group in which mammography becomes the primary screening method[29].

A comparative analysis using a simulation model of pathogenic variants in *BRCA1* and *BRCA2* demonstrated that annual MRI from 25 years old onwards, accompanied by alternating digital mammography from the age of 30 onwards, is probably the most effective screening strategy, being related to the highest life expectancy[33].

According to data in the literature, when MRI and mammography were combined, the sensitivity goes up to 93%. Women with previous breast cancer are at greater risk of developing secondary tumors in the treated and contralateral breast; therefore, the combined use of imaging tests is also recommended[30].

Guidelines for MRI screening in women with moderate penetrance pathogenic variants are also not so well defined. Annual MRI is considered for patients with variants in *ATM*, *CHEK2* and *NBN* from the age of 40 onwards, and the age of 30 onwards for patients presenting variants in *PALB2, CDH1* and *NF1*[29].

Recommendations for discontinuing MRI screening in patients at increased risk vary between age groups over 50 years old — except for patients with dense breasts —, and after the age of 75 or when the life expectancy of the patient is set at less than 10 years[10,29].

Ultrasonography, although not used as a routine method, can be useful as a complementary method in selected patients. Sensitivity is lower than that of MRI but comparable to that of mammography in young patients at increased risk. Therefore, in this group, it may be indicated mainly in women with dense breasts, pregnant women, lactating women or women who cannot undergo MRI[29].

Although it does not provide many additional benefits in detecting cancer, the ultrasound can be used to increase the specificity of MRI by ruling out benign lesions. Furthermore, its adjuvant use may be more convenient and economical for short-term follow-up and also in guided biopsies[30].

Although breast cancer is more common among women, men who carry mutations in the *BRCA2* gene may be at increased risk of developing the disease. In this case, annual clinical breast exam and monthly self-examination are recommended from the age of 35 onwards. Due to the low incidence of breast cancer in this group, even in those at increased risk, there are no studies to determine the value of additional screening methods[29].

Genetic counseling and molecular research

Genetic counseling is a multifaceted process that can help to identify patients and family members who carry a mutation associated with increased risk of cancer. Genetic research should always be accompanied by pre- and post-test counseling, as to clarify all the possibilities of results, the limitations of the tests to be performed, and the possibilities of prevention, as well as to present the follow-up strategies and evaluate the chances of disease occurrence or recurrence in patients or relatives[34].

International cancer research bodies propose guidelines that alert experts to pay attention to individuals at increased risk of hereditary cancers[35].

According to guidelines by the National Comprehensive Cancer Network (NCCN), individuals who meet at least one of the following criteria should be referred for genetic counseling: personal history of breast and/or ovarian cancer; diagnosis under 50 years of age (in case of triple-negative breast cancer, personal history of two breast cancer diagnoses regardless of age of onset, and known mutation in a cancer-susceptibility gene within the family); several close family members with related cancers (breast, ovary, colon, endometrial, prostate, or pancreatic); diagnosis of breast cancer in men; and people of Ashkenazi Jewish ancestry with personal history of breast, ovarian and/or pancreatic cancer[10].

In recent years, genetic testing has been allied to clinical practice. Until recently, the test was mainly performed by patients with a prominent family history of cancer encompassing a limited number of genes associated with a high or moderate risk of hereditary cancer. With the advent of the Next Generation Sequencing (NGS) molecular technique, panel genetic testing has become more widely used[36].

Thus, there is scientific evidence of a clear association between hereditary cancer and some gene groups of high and moderate penetrance, with the presence of pathogenic variants that bring some possibilities of interference in therapeutics and disease management. In addition, the tracking of family members not yet affected by the disease is possible[10].

The largest Brazilian study carried out by Palmero et al. sought to identify recurrent mutations in *BRCA1* and *BRCA2* that could be included in a low-cost genetic panel used as screening method for patients with predisposition to hereditary cancer. The study was carried out based on 649 genetic tests with pathogenic or probable pathogenic variants, obtained from 28 public and private health centers from 11 Brazilian states. In total, 126 mutations were identified in the *BRCA1* gene and 103 in the *BRCA2* gene, with 26 new variants identified in both genes[19].

Table 1 lists some of the most prevalent mutations identified by the study.

However, some mutations were reported exclusively in certain geographic regions of the country, which suggests their founder effect and highlights the huge molecular heterogeneity and limited knowledge about these genes in the Brazilian population[19].

Table 1. Mutations identified by Palmero et al.[19] in at least three probands

BRCA1	n (%)	*BRCA2*	n (%)
c.5266dupC	89 (20.2)	c.2808_2811delACAA	20 (9.6)
c.3331_3334delCAAG	45 (10.2)	c.5946delT	15 (7.2)
c.68_69delAG	19 (4.3)	c.156_157insAlu	11 (5.3)
c.211A>G	17 (3.9)	c.6405_6409delCTTAA	10 (4.8)
c.5074+2T>C	14 (3.2)	c.2T>G	8 (3.8)
c.470_471delCT	11 (2.5)	c.1138delA	7 (3.4)
c.1687C>T	10 (2.3)	c.9382C>T	7 (3.4)
c.4675+1G>A	9 (2.0)	c.2266C>T	3 (1.4)

Source: prepared by the authors based on data taken from the article by Palmero et al.[19]

To date, more than 35 candidate genes related to high and moderate risk of breast cancer have been suggested[9,28]. However, only few of these known genes had their variants significantly associated with breast cancer susceptibility, even in cases of positive family history or early diagnosis of the disease[9,37].

By the same token, the use of multigene panels in genetic tests has considerably increased the number of patients diagnosed with a variant of uncertain significance (VUS), which reinforces the need for better models predictive of pathogenicity and increased efforts to help classify these variants, such as co-segregation analyses, personal and family history, co-occurrence of pathogenic variants, and histological and molecular characteristics of tumors[9,38].

In order to better define the set of genes associated with breast cancer risk, Dorling et al. created a panel with 34 known genes that show an association with or susceptibility to breast cancer. The study included women with (60,466) and without breast cancer (53,461) from 25 countries who took part in population-based studies and studies based on families with a history of breast cancer, making up the Breast Cancer Association Consortium (BCAC)[36].

Variants that cause alteration in protein function were associated with a significant risk of breast cancer ($p<0.0001$) in 5 genes: *ATM, BRCA1, BRCA2, CHEK2* and *PALB2* (95%CI 2.10–10.57). Susceptibility to breast cancer was also observed in 7 genes: *BARD1* (OR=2.09; 95%CI 1.35–3.23), *RAD51C* (OR=1.93; 95%CI 1.20–3, 11), *RAD51D* (OR=1.80; 95%CI 1.11–2.93), *PTEN* (OR=2.25; 95%CI 0.85–6.00), *NF1* (OR=1.76; 95%CI 0.96–3.21), *TP53* (OR=3.06; 95%CI 0.63–14.91) and *MSH6* (OR=1.96; 95%CI 1.15–3.33) (Table 2)[36].

Table 2. The 34 genes in the study by Dorling et al.[36]

ABRAXAS1	*MSH2*
AKT1	*MSH6*
ATM	*MUTYH*
BABAM2	*NBN*
BARD1	*NF1*
BRCA1	*PALB2*
BRCA2	*PIK3CA*
BRIP1	*PMS2*
CDH1	*PTEN*
CHEK2	*RAD50*
EPCAM	*RAD51C*
FANCC	*RAD51D*
FANCM	*RECQL*
GEN1	*RINT1*
MEN1	*STK11*
MLH1	*TP53*
MRE11	*XRCC2*

Source: prepared by the authors based on data taken from the article by Dorling et al.[19]

Following similar objectives, the North American study conducted by Hu et al. involving 12 population-based studies used a panel with 28 breast cancer-predisposing genes evaluated in 32,247 case-patients and 32,544 control-patients (Table 3)[37-39].

Pathogenic variants were identified in 12 genes established as predisposing to breast cancer in 5.03% of cases and 1.63% of controls. Corroborating the study by Dorling et al., the *BRCA1* (OR=7.62; 95%CI 5.33–11.27) and *BRCA2* (OR=5.23; 95%CI 4.09–6.77) genes are linked to a high risk for breast cancer; and the *PALB2* (OR=3.83; 95%CI 2.68–5.63) and *CHEK2* (OR=2.47; 95%CI 2.02–3.05) genes, to moderate risk[36].

In women affected by the disease, the most prevalent mutations were observed in *BRCA1* (OR=7.62; 95%CI 5.33–11.27), *BRCA2* (OR=5.23; 95%CI 4.09–6.77) and *PALB2* (OR=3.83; 95%CI 2.68–5.63). In unaffected women, most mutations were observed in *CHEK2* and *ATM*, indicating a moderate risk for breast cancer[39].

In summary, both studies showed a significant association between breast cancer risk and variants of 8 genes — *BRCA1, BRCA2, PALB2, BARD1, RAD51C, ATM* and *CHEK2*. However, most genes tested were not significantly associated with breast cancer, and the larger the multigene panel, the higher the VUS rates[36,39].

Women who carry mutations in *CHEK2* and *ATM* have tumors that express estrogen receptors, which may benefit from anti-estrogen therapies such as tamoxifen, raloxifene or aromatase inhibitors. However, studies involving chemoprevention have not been carried out in women with mutations in *CHEK2* or *ATM*; and even among carriers of mutations in *BRCA1* and *BRCA2*, the absorption of tamoxifen is low[40].

With regard to other types of cancer, carriers of *CHEK2* mutations are considered to be at high risk for colon cancer, and carriers of *ATM* mutations are considered at risk for pancreatic

Table 3. The 28 genes in the study by Hu et al.[39]

ATM	*MRE11A*
BARD1	*MSH2*
BLM	*MSH6*
BRCA1	*NBN*
BRCA2	*NF1*
BRIP1	*PALB2*
CDH1	*PTEN*
CDKN2A	*RAD50*
CHEK2	*RAD51C*
ERCC3	*RAD51D*
FANCC	*RECQL*
FANCM	*RINT1*
MLH1	*SLX4*
XRCC2	*TP53*

Source: prepared by the authors based on data taken from the article by Hu et al.[39]

cancer. However, colon cancer screening is recommended for carriers of *CHEK2* mutations, but not for *ATM* mutation carriers when it comes to pancreatic cancer in[10].

It is important to emphasize that the use of genetic panels and analyses of genomic rearrangements are great allies in the investigation of hereditarily-predisposed cancer, and that panels with multiple investigated genes must be well evaluated, as they can generate data for which clinical management has not yet been determined and, therefore, some patients may choose to have a genetic test with a smaller panel of genes, containing only high and moderate risk genes, as these provide the best-characterized cancer risk estimates and management recommendations[41].

Table 4 presents nine genes associated with breast cancer risk, including estimated lifetime risk, other malignancies associated with the presence of gene mutations, and individualized management and screening approaches according to NCCN guidelines[10], as well as data presented in studies by Dorling et al.[36], Bharucha et al.[42], Owens et al.[35] and Shiovitz et al.[28].

Genes known to be associated with high and moderate risk of breast cancer are frequently mentioned in the scientific literature[6,43,44] while likely candidate genes for hereditary breast cancer susceptibility are investigated. The study by Torrezan et al. analyzed 23 of these genes in 42 women evaluated for increased risk of hereditary breast cancer from a South American hospital cohort, with no identified variants in the *BRCA1, BRCA2, TP53* and *CHEK2* genes (c.1100delC). However, possible deleterious variants were identified in 12 new candidate genes associated with hereditary cancer, also evaluated in previous studies: *NOTCH2, DNAH7, RAF1, MST1R, LAMB4, NIN, SLX4, ERCC1, SLC22A16, PTPRD, ARHGEF12* and *ERBB2*[9].

These findings provide a set of new genes that can be reanalyzed, bringing new evidence of a possible breast carcinoma phenotype, including case-control studies in different populations, especially in cases where there is strong evidence for hereditary predisposition and no variant that justify the clinical phenotype[9,45].

Table 4. Pathogenic mutations in high- and moderate-risk genes associated with breast cancer

Germline mutation	Cumulative risk* of breast cancer	Other associated malignancies	Screening guidelines†
BRCA1	85%	Ovary, fallopian tubes, peritoneum, pancreas, prostate, colon.	25-29 years‡: Annual MRI (mammography if MRI is not available); 30–75 years: annual mammography and MRI; discuss preventive mastectomy and bilateral salpingo-oophorectomy after pregnancy.
BRCA2	65%	Ovary, fallopian tubes, peritoneum, pancreas, prostate, melanoma.	25-29 years‡: Annual MRI (mammography if MRI is not available); 30–75 years: annual mammography and MRI; discuss preventive mastectomy and bilateral salpingo-oophorectomy after pregnancy.
TP53	85%	Sarcomas and CNS, adrenocortical, gastrointestinal, and associated with radiation.	25–29 years‡: Annual MRI (mammography if MRI is not available); 30–75 years: annual mammography and MRI; discuss bilateral preventive mastectomy.
PTEN	67–87%	Thyroid, endometrium, colorectal, renal.	30–35 years‡: Annual MRI and mammography; discuss preventive mastectomy.
CDH1	42–60%	Diffuse gastric cancer.	30 years or older: annual mammography, consider annual MRI; insufficient evidence for preventive mastectomy
STK11§	44–50%	Colorectal, stomach, small intestine, pancreas, ovary, Sertoli cell tumor.	25–29 years‡: Annual MRI; 30 years and older: annual mammography and MRI.
ATM	20%	Pancreas.	≥40 years: annual mammography; consider annual MRI; insufficient evidence for preventive mastectomy, or prescription of radiation therapy.
CHEK2	20–25%	Colorectal, stomach, prostate, kidney and thyroid.	≥40 years: annual mammography; consider annual MRI; insufficient evidence for preventive mastectomy.
PALB2	33%–59%	Pancreas.	≥30 years: annual mammography and MRI; insufficient evidence for preventive mastectomy.

MRI: magnetic resonance imaging; CNS: central nervous system. *Estimated cumulative risk up to 70 years of age; †Due to a lack of local studies, the recommendations in Brazil are based on international data; ‡Or 10 years before the youngest person affected in the family; §Gene evaluated in the study by Dorling et al.[36], but without statistical significance of risk.
Source: Prepared by the authors, based on information taken and adapted from[10,28,35,36,42].

Therapeutic and risk-reducing approaches in hereditary breast cancer

The term "risk reduction" has been considered more appropriate than "prophylactic" in recent times, as no mastectomy can remove all of the breast tissue. Studies have shown a reduction in breast cancer risk of approximately 95% in *BRCA1* and *BRCA2* mutation carriers undergoing bilateral risk-reducing mastectomy (BRRM) in combination with oophorectomy, and a reduction in risk of approximately 90% in those with intact ovaries[46-48].

A recent systematic review confirms the benefit of BRRM in reducing breast cancer incidence and mortality in patients at high risk for breast cancer predisposition such as carriers of *BRCA1* and *BRCA2* mutations, but this evidence requires rigorous prospective studies due to methodological flaws in the existing literature[49]. Contralateral mastectomy as risk reduction (CMRR) data for patients who had unilateral breast cancer are not conclusive, as existing studies show a reduction in the incidence of contralateral breast cancer but no definitive survival benefit[50-53].

The main treatment strategies for breast cancer are surgery and systemic treatment. One of the main concerns in the surgical treatment of breast cancer with a pathogenic variant for *BRCA1* and *BRCA2* is whether the outcome of treatment with breast-conserving surgery (BCS) combined with adjuvant radiotherapy is equivalent to radical mastectomy[54].

A study compared results of the surgical method (BCS combined with radiotherapy *versus* mastectomy) in cases of breast cancer with pathogenic variants *BRCA1* and *BRCA2*. According to the work by Onitilo et al., a higher 10-year survival was observed in the group undergoing BCS with adjuvant radiotherapy (BCS: 80.9% *versus* mastectomy: 67.2%), in addition to lower rates of local recurrence[54].

However, it is known that women who carry mutations in *BRCA1* and *BRCA2* are more likely to develop a secondary cancer, that is, ipsilateral or in the contralateral breast. For these patients, a bilateral mastectomy is recommended, as studies suggest that women who carry mutations in *BRCA1* and *BRCA2* and who undergo bilateral mastectomy are less likely to die of breast cancer than women who have been treated with unilateral mastectomy[46-52].

A meta-analysis encompassing 526 patients with a pathogenic variant in *BRCA1* and *BRCA2* and 2,320 patients with sporadic breast cancer showed no difference in overall survival rates between these groups. However, patients with mutations in *BRCA1* and *BRCA2* had a greater recurrence of ipsilateral breast cancer than patients with sporadic breast cancer, with a mean follow-up of more than six years (RR=1.51; 95%CI 1.15–1.98)[55].

Radiation after BCS is not performed only in very exceptional cases. Given the essential role of the *BRCA1* and *BRCA2* genes in DNA repair of other cancer-inducing genes in humans, questions have been raised regarding the possible complications of radiotherapy in breast cancer involving pathogenic variants in *BRCA1* and *BRCA2*[15]. However, a study by Pierce et al. showed no significant difference in radiation complication rates between women carrying *BRCA1* and *BRCA2* mutations *versus* women with sporadic cancer[56].

In this setting, radiotherapy also plays an important role after mastectomy. Indications should be similar in both radical surgery and conservative mastectomy. Traditionally, radiotherapy is indicated for patients with four or more affected lymph nodes, positive surgical margins, or with tumors larger than 5 cm. However, there is a debate about the role of radiotherapy in patients with 1–3 metastatic lymph nodes and the role of secondary factors such as age, molecular subtype and angiolymphatic invasion in the decision-making about the use of radiotherapy after mastectomy, remaining quite controversial[48].

In patients with the Li-Fraumeni syndrome presenting with germline mutations in the *TP53* gene, exposure to radiotherapy increases the risk of a second cancer. In these patients there is an inactivation of DNA repair mechanisms and activation of apoptosis, so the susceptibility to radio-induced tumors can accelerate the appearance of a second neoplasm[57].

The repair pathway by homologous recombination of damaged DNA — in which there is loss of function caused by mutations present in the *BRCA1* and *BRCA2* genes — lead to very similar phenotypes, which fall within the hereditary predisposition to breast and ovarian cancer. Likewise, mutations in *RAD51C*, *BRIP1, PALB2* and others can lead to a phenotype similar to that of HBOC[58].

By taking into account the chemotherapy-based treatment, which causes DNA damage requiring repair genes of the homologous recombination pathway to induce a repair response, the status of the pathogenic variant in *BRCA1* and *BRCA2* is considered a decisive factor to predict sensitivity to chemotherapy[15].

The profile of genomic structural alterations caused specifically by homologous recombination deficiency (HRD) repair has been studied as potential markers of pathway deficiency through scores, which may be useful in evaluating the association not only with the response rate to chemotherapy, but also with clinicopathological and overall survival factors[59].

In *in vitro* studies, cells with the *BRCA1* variant were shown to be more sensitive to platinum-based chemotherapeutic agents, as they disrupt the DNA structure. They also showed greater resistance to microtubule-inhibiting chemotherapies such as taxanes. These findings were supported by data from patients with *BRCA1* and *BRCA2* pathogenic variant breast cancer who underwent palliative or neoadjuvant taxane-only chemotherapy[50]. However, there is insufficient evidence to exclude taxanes from adjuvant chemotherapy strategies in patients with breast cancer carrying mutations in *BRCA1* and *BRCA2*[15].

Patients diagnosed with breast cancer at younger ages and carriers of mutations in high and moderate penetrance genes should have an individualized surgical treatment. Carriers of

BRCA1 and *BRCA2* mutations, for example, face more aggressive surgical interventions for therapeutic purposes and to reduce the risk of developing primary or contralateral breast cancer, which is increased[57].

However, breast-conserving surgery, as well as skin-sparing mastectomies with or without preservation of the nipple-areolar complex, have been shown safe and to provide a better restoration. Selecting the best surgical approach for this group of patients requires taking into account several factors, including genetic risk, personal and family history, and the patient's own preferences[57].

AUTHORS' CONTRIBUTIONS

R.M.F: conceptualization, investigation, formal analysis, writing – original. P.M.: investigation, formal analysis, writing – original. M.R.G.: writing – review & editing. M.T.B.T: writing – review & editing.

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REVIEW ARTICLE
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Breast reconstruction and radiotherapy: a literature review

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ABSTRACT

Breast cancer is the most common malignancy in women worldwide. After mastectomy, many women wish to reconstruct the affected breast and immediate breast reconstruction has been proven oncologically safe compared to mastectomy only. In addition, indications for post-mastectomy radiotherapy (PMRT) sessions are becoming more frequent, due to their relationship with reduced mortality and locoregional recurrence. For this reason, many women who opted for immediate reconstruction underwent radiotherapy with implants or expanders. The objective of this study was to compare the outcome of patients with breast cancer undergoing adjuvant radiotherapy after breast reconstruction with an implant or expander with that of patients who did not need irradiation. A literature review was carried out on the CAPES Journal Portal. The studies are unanimous when it comes to the increased risk of complications between control groups and patients who have undergone PMRT. Reconstruction failure rates were lower and the esthetic results were better in surgeries with implants compared with tissue expanders. Autologous surgeries are apparently safe and should be considered in the context of PMRT. This review did not find sufficient scientific evidence to determine the best technique and the best period for radiotherapy in PMRT indications. The choice of the surgical technique and the time of radiotherapy must be at the discretion of the surgeon and multidisciplinary team of each service, always in a shared decision with the patient.

KEYWORDS: breast cancer; mammaplasty; breast implants; radiotherapy, adjuvant; surgical flaps.

INTRODUCTION

Breast cancer is one of the most common malignancies in women and one of the three most common cancer types worldwide. Most women that undergo mastectomy are candidate for reconstruction of the mutilated breast, either immediately or at a later moment. Immediate breast reconstruction, that is, performed at the same time as the mastectomy, has been proven safe from an oncological point of view when considering local recurrence and long-term survival. In addition, the psychological, self-esteem, financial and esthetic benefits compared to other procedures should be taken in consideration.

As a general rule, two techniques using heterologous materials are widely used in immediate reconstructions (breast prostheses or implants and tissue expanders). The first one is the implant itself, the other is a two-step reconstruction in which a tissue expander is implanted during mastectomy (step 1), its expansion is performed during the postoperative period and, later, the permanent implant is inserted (step 2).

Referrals for post-mastectomy radiotherapy (PMRT) sessions have become more frequent due to their relation with reduced mortality and locoregional recurrence in women with breast cancer. The referral to radiotherapy is not a routine, and a set of information including data on pathological anatomy and other histopathological parameters is necessary for a more assertive diagnosis and management. Thus, many women with an indication for immediate heterologous breast reconstruction underwent adjuvant radiotherapy in implants or expanders that had already been inserted.

This work aims to analyze and discuss, through a review of the recent literature, the effects and outcomes of radiotherapy in women who underwent heterologous breast reconstruction immediately after mastectomy.

OBJECTIVES

To compare the outcomes of patients with breast cancer undergoing adjuvant radiotherapy after breast reconstruction with definitive implant or tissue expander with that of patients who had no indication for adjuvant radiotherapy.

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METHODS

Selection — inclusion and exclusion criteria

All studies addressing the outcome of patients with breast cancer undergoing or not adjuvant radiotherapy after breast reconstruction surgery with an implant or tissue expander were considered, whether performed in one or two stages. Studies that considered only autologous augmentation were also used with the purpose of comparison and enrichment of this paper.

Database

The search was carried out in the PubMed database and Capes Journal Portal.

Descriptors

The descriptors used were: Postmastectomy Radiotherapy AND implant-based reconstruction; Postmastectomy Radiotherapy AND TRAM; Postmastectomy Radiotherapy AND latissimus dorsi.

Time limit and language

Articles published between 2014 and 2020 in English and Portuguese were selected.

Research phases

We found 128 articles during the research, then we did an exploratory reading. As a result, we selected 42 articles for selective reading and 18 articles were finally chosen as matching the goals and subjects of this study; analytical reading and analysis of texts, with interpretative reading, compilation of relevant results and, finally, writing (Figure 1).

RESULTS

The definition of reconstruction failure mentioned in the articles was permanent removal of the tissue expander (TE) or permanent implant (PI) without replacement or conversion to autologous augmentation or secondary absence of breast reconstruction[1].

Most of the results of the analyzed articles showed that the chances of failure in reconstructions are greater after a radiotherapy session, for those who used both a tissue expander or a permanent implant when compared with patients who underwent reconstruction and did not receive radiotherapy. These data support the relevance of a longitudinal and close follow-up of these patients, since PMRT is still the standard adjuvant therapy for patients who opted for immediate breast reconstruction with an implant[2].

When comparing PMRT for patients that underwent breast reconstruction with a tissue expander versus PMRT with a permanent implant, Cordeiro et al. demonstrated that radiation on tissue expanders increased the rate of failures and complications compared to permanent implants (32% versus 16.4% in six years of follow-up; $p < 0.01$). On the other hand, esthetic results and satisfaction with the reconstruction were higher among patients who exchanged the tissue expander for the definitive implant after radiotherapy[3].

Another study came to the same conclusion as above, but stating that patients with a history of depression had a significant increase in complication rates for both tissue expanders and permanent implants[4].

Furthermore, when comparing non-irradiated patients with patients undergoing tissue expander radiotherapy or permanent implant radiotherapy, the reconstruction failure rate is significantly lower among non-irradiated women, with a reduction of 5.5% ($p < 0.01$)[3].

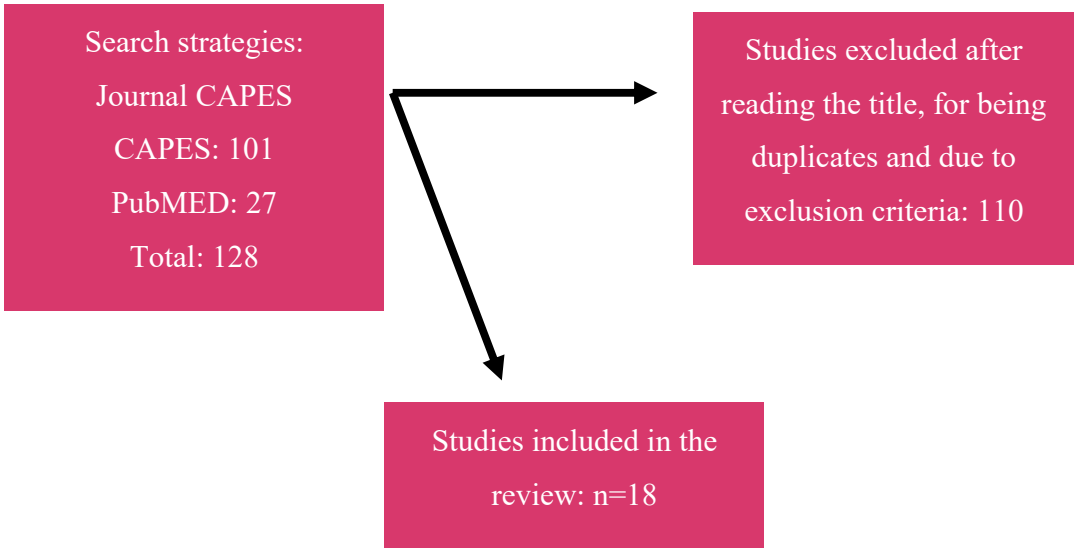

Figure 1. Descriptive flowchart of selection process.

The pathogenesis of capsular contracture is not well understood. It is a multifactorial process that involves a reaction in the human body, with the formation of a biofilm, and also a possible colonization of the implant by bacteria[5].

Moreover, patients that underwent radiation on tissue expanders had a better proportion of good esthetic outcomes compared to patients with permanent implants (75.0% versus 67.6%; $p < 0.01$) and lower rates of grade IV capsular contracture ($p < 0.01$), which is considered severe and indicates an unacceptable result and/or painful symptomatology, requiring new surgical intervention[3,5].

Patients that did not have any reconstructive failures had varied proportions of capsular contracture according to the type of procedure adopted after mastectomy: grade III capsular contracture was present in 3.7% of implants without radiotherapy; 15.9% of patients who received radiotherapy with tissue expander; and 44.6% of patients who received radiotherapy with permanent implant ($p < 0.01$). Grade IV capsular contracture was present in 0.4%, 1.22% and 6.3% of the groups mentioned, respectively[3].

In another study, Barry and Kell[6] demonstrated that immediate implant reconstruction in patients who received radiotherapy have a significantly higher incidence of complications compared to those who did not receive radiotherapy. This is not surprising, as radiotherapy treatment can affect the esthetic result and cause an increase in postoperative complications, in addition to having its effectiveness impaired when done immediately after breast reconstruction.

According to Barry and Kell immediate breast reconstruction after skin sparing mastectomy offers a number of advantages over delayed reconstruction. Firstly, it provides better esthetic results due to the preservation of the infra-mammary fold and skin envelope, allowing for a more natural appearance and the possibility of adjusting the surgical scar position. In addition, for the patient, it restores femininity and improves vitality, sexuality and quality of life, while avoiding or recovering resulting depressive conditions[6].

In a recent study, Lam et al. analyzed, between 1998 and 2010, 452 patients who underwent immediate breast reconstruction in two stages, involving a total of 562 breasts. The first phase was defined as the insertion of temporary expander and, the second one, as the insertion of permanent implant. Postoperative adjuvant radiotherapy was recommended on the tissue expander in situ for 114 patients. Overall postoperative prosthesis loss was 2.7%. For patients undergoing adjuvant chemotherapy, the loss was 5.3%, increasing to 11.3% for patients receiving chemotherapy and radiotherapy. Chemotherapy and radiotherapy were the main risk factors, with a statistically significant result of loss of expander or breast implant; RR: 13.85 ($p = 0.012$) and 2.23 ($p = 0.027$), respectively. Prosthesis loss for patients undergoing chemotherapy combined with radiotherapy was also significant; IRR: 4,791 ($p < 0.001$)[7].

Also from 2018, a meta-analytic study conducted in China by Pu et al., demonstrated that the use of PMRT increased the failure rate of breast implant reconstruction [odds ratio (OR): 2.59; 95%CI 1.46–4.62; $p = 0.001$]. Heterogeneity was considered significant [$I2 = 73\%$, $\chi^2 = 33.39$ ($df = 9$), $p = 0.001$][2].

When dealing with the technique of breast reconstruction with transversus abdominis muscle (TRAM) flap, Lee et al. compared the long-term results of PMRT among breast cancer patients with and without immediate myocutaneous flap reconstruction. A total of 492 patients were assessed, of which 213 underwent reconstruction with the TRAM technique. The results suggested that immediate reconstruction with TRAM flap does not compromise long-term clinical outcomes in breast cancer patients requiring PMRT. There was no statistically significant difference in rates of local recurrence, distant metastases, disease-free survival and overall survival when comparing immediate TRAM flap reconstruction with no reconstruction[8].

In contrast, Rochlin et al. compared the effect of PMRT on TRAM reconstruction. In a literature review, they evaluated the evidence from all fields involved in the care of patients with breast cancer, in order to advance a recommendation on this therapeutic sequence. Eleven retrospective studies with 337 patients with an average follow-up of 18–60 months were included. These authors found an increased probability of fat necrosis in the irradiated breast (OR = 3.13, 95%CI 1.42–6.89, $p = 0.005$) in three studies with non-irradiated controls and five studies that evaluated the estheticoutcome with varying results. The final conclusion is that additional prospective studies are needed, since current evidence is contradictory[9].

Regarding the technique of breast reconstruction using the *latissimus dorsi* myocutaneous flap, Carrabin et al. compared and evaluated the results of breast reconstruction with *latissimus dorsi* muscle without implant followed by adjuvant radiotherapy. Thirty-one patients with irradiated reconstructions performed between 1999 and 2013 were assessed. Two individuals died in the period. Breast reconstruction results were rated as very good or good in 86% of cases, with reconstructed breast consistency evaluated as very good or good in 93% of cases. The authors considered the technique had good tolerance to adjuvant irradiation and could be used in patients willing to benefit from immediate reconstruction and with an indication for subsequent radiotherapy[10].

Following the technique of breast reconstruction with *latissimus dorsi* muscle, Yun et al. demonstrated that according to a systematic review of patients treated with PMRT with or without adjuvant chemotherapy from 2000 to 2015, there was a significantly higher weighted incidence of reoperation (37.0% versus 16.6%, $p < 0.0001$), global complications (41.3% versus 30.9%, $p < 0.0001$), and reconstructive failure (16.8% versus 1.6%, $p < 0.0001$) in patients undergoing breast reconstruction with definitive implants when compared to reconstruction with autologous

material[11,12]. A single study comparing immediate *latissimus dorsi* flap with tissue expander reconstruction after mastectomy followed by PMRT found a trend of surgical wound complications requiring reoperation in the tissue expander group, concluding that immediate *latissimus dorsi* flap reconstruction is a viable and safe option for patients undergoing PMRT[13]. In the subset of patients who received pre-mastectomy total breast radiotherapy, studies show a significant increase in the risk of complications associated with the use of tissue expander-based reconstruction, and autologous or myocutaneous flap reconstruction is strongly recommended[14,15].

A recent study by Chiasson et al. involved a two-phase approach using *latissimus dorsi* myocutaneous flaps and tissue expanders for immediate reconstruction after mastectomy, followed by replacement with implants in a secondary surgery. A retrospective review was performed on 201 medical records (376 breast reconstructions) of patients who met the inclusion criteria. Reconstructive success was defined as no need for additional autologous reconstruction beyond the two-stage approach. When analyzing the complications and final outcomes, there was no difference between non-irradiated and irradiated patients, except when reconstructive loss was observed (3.6% rate in the non-irradiated group and 16.6% in the irradiated group, p = 0.03). However, one third of the cases of reconstructive losses among patients in the irradiated group were due to reasons unrelated to radiotherapy. Taking this into account, overall reconstructive success was not statisticaly significant when comparing groups. The findings of this study show that immediate reconstruction with *latissimus dorsi* myocutaneous flaps in conjunction with prosthetic devices is reliable and safe even in the setting of adjuvant radiotherapy, as the autologous tissue attenuates many of the sequelae of radiotherapy itself. This type of reconstruction not only provides an esthetically pleasing two-stage outcome, but also has a favorable complication profile and a very acceptable success rate[16].

A relatively simple procedure that is increasingly being recognized as a strategy in the irradiated patient is autologous lipotransfer or fat grafting. Regarding this technique, Ribuffo et al. *apud* Crawford and Endara presented a series of 32 patients who underwent modified radical mastectomy followed by radiotherapy. The patients were immediately reconstructed with placement of a tissue expander in the submuscular plane. Half of the patients underwent one or two procedures complemented with autologous lipotransfer six weeks after the completion of radiotherapy, before exchanging the expander for the definitive implant. There was a 0% complication rate in the treated group and a 43% rate in the control group. The introduction of lipotransfer as a separate but necessary procedure within the protocol was unique and became a formal piece and fundamental factor for the success of this procedure[17,18].

Another study by Serra-Renom et al. *apud* Crawford and Endara confirmed the usefulness of lipotransfer in 65 irradiated and mastectomized patients, incorporating serial fat grafts in their protocol. These patients underwent multiple fat grafting procedures, before and at the time of exchanging the expander with the implant, with excellent clinical results. This study had limitations, as patients were not demonstrating significant acute effects of radiation in the form of radiodermatitis and, therefore, the severity of tissue damage was in question[17,19].

In a systematic review, Oliver et al. gathered 11 studies with data from 1,565 procedures for immediate breast reconstruction (IBR) with a double-stage expander, where PMRT was employed. Of the total, 1,145 were irradiated before replacement of the tissue expander and 420 were irradiated after inclusion of the definitive implant. There was a statistically significant higher probability of surgical bed infection with the addition of radiotherapy before permanent implant placement (21.03%, p = 0.000079), compared with PMRT after implant placement (9.69%).There was no significant difference in the explantation rate between PMRT performed before definitive implant placement (12.93%) compared to those who performed PMRT after definitive implant placement (11.43%)[20]. A retrospective study[21] evaluated 4,068 patients in a prospectively collected database that included 2,284 patients, or 3,489 breasts, who met the study's inclusion criteria. Most patients had bilateral reconstruction [n = 1,215 (53.5%)] with silicone implants [n = 1,244 (54.5%)]. Three hundred twenty-three patients (14%) underwent some form of radiation therapy as part of their breast cancer treatment. Eighty-seven patients (3.8%) underwent radiotherapy before reconstruction, and the remainder underwent adjuvant radiation therapy of their tissue expanders [n = 43 (1.9%)] or permanent implant [n = 193 (8.4%)]. Esthetic outcomes over time were compared and evaluated for patients over a 12-year period. Patients were then subdivided to analyze long-term trends into distinct reconstructive groups. In general, patients with bilateral reconstructions had significantly higher esthetic scores compared to unilateral reconstruction, and this trend continued over time (p < 0.001). Further comparison of patients undergoing or not radiotherapy had a similar consistency, with better esthetic ratings between non-irradiated than bilateral irradiated reconstructions over the first 9 years of follow-up (p < 0.05). Unilaterally irradiated reconstructions had lower esthetic scores among all patients during the full 12-year follow-up period (p < 0.05). Capsular contracture rates were assessed in all reconstructed breasts similarly between irradiated and non-irradiated patients. Irradiated and reconstructed breasts had higher rates of capsular contracture than non-irradiated breasts at all time points evaluated (p < 0.001). Interestingly, both groups demonstrated the inflection point in the score, with a significant drop in mean scores for non-irradiated patients [1.38 (year 2) to 1.1 (year 3)] and also for

irradiated patients [2.21 (year 3) to 1.82 (year 4)] ($p < 0.05$). These decreases in scores for capsular contracture were maintained for the remainder of the study follow-up period. The data visibly demonstrate the stability over time in the results reported by the surgeon regarding esthetic outcomes and the degree of capsular contracture following the technique of breast reconstruction based on breast implants. In the period from year 1 to year 12 of follow-up, scores for esthetic results between all techniques of bilateral reconstructions (4.73 ± 0.64 to 4.44 ± 0.82; $p < 0.0001$) and unilateral reconstructions (4.02 ± 0.91 to 3.63 ± 0.99; $p = 0.0005$) had an overall decrease. Although these downward trends were statistically significant, because of the statistical power of individual groups, the clinical difference in scores ranged from 0.29 to 0.39 with overlapping confidence intervals. Likewise, the capsular contracture rate remained clinically and statistically stable throughout the study period for non-irradiated (year 1, 1.27 ± 0.53; year 12, 1.23 ± 0.54; $p = 0.37$) and irradiated breasts (year 1, 1.92 ± 0.89; year 12, 1.66 ± 0.87; $p = 0.12$).

A subset analysis of all patients with outcome data reported and analyzed by the BREAST-Q was performed based on breast irradiation status. Regarding satisfaction, non-irradiated patients reported significantly better results than irradiated patients during the first six years. On the other hand, when it comes to satisfaction with the overall results of the surgery, non-irradiated and irradiated patients showed no significant difference, except in the first year. A similar trend was observed by case reports of patients as to psychosocial and sexual well-being over time, with a normalization of scores between non-irradiated and irradiated patients after the first year of implant replacement. Physical well-being appears to mirror the trend of breast satisfaction, with non-irradiated patients scoring significantly higher than irradiated patients through year 6, at which time scores among irradiated patients improved. Similarly to the stability observed in the results described by the surgeon over time, the patients' reports on the surgeries demonstrated visible stability in the scores, with an improvement over the same period. There was no overall worsening in patient-reported outcomes for any category measured over the 12-year study period. In particular, breast satisfaction and psychosocial well-being scores did not change. Satisfaction with the results increased significantly over time among all patients (70.9 ± 20.9 versus 76.9 ± 16.4; $p = 0.03$), reaching the minimum important difference in the irradiated patients in year 1 to year 12. Concerning sexual well-being, scores remained statistically similar over time; however, a comparison between year 1 and year 12 reached the minimum important difference among all patients. Meanwhile, physical well-being scores showed significant improvement (72.8 ± 16.2 versus 82.8 ± 15.5; $p < 0.0001$) in non-irradiated (74.1 ± 15.9 versus 83.2 ± 15.4; $p = 0.0002$) and irradiated patients (67.7 ± 16.5 versus 81.0 ± 17.2; $p = 0.02$)[21] (Table 1).

DISCUSSION

Most studies are retrospective, which conditions the results to the accuracy and availability of information. The assessment based on different characteristics and outcomes such as implant loss, capsular contracture and infection are objective and allow for a clearer view and a more detailed analysis of data. However, aspects such as esthetic results and satisfaction after surgery can be considered ambiguous and, therefore, potentially confusing factors.

The studies are unanimous when it comes to the increased risk of complications between control groups and patients undergoing PMRT. In all studies that considered patients with and without radiotherapy after breast reconstruction, the group undergoing PMRT had a higher rate of adversities[4,7]. Studies have showed no significant difference as for the timing of radiotherapy[1].

As for the technique used, some studies compared permanent implants with tissue expanders, and the global reconstructive failure rates were lower and with better esthetic results in surgeries with definitive breast implants[3]. An important aspect identified in the literature is that in double-stage breast reconstruction with an indication for PMRT, irradiation after replacing the expander with the definitive implant has a lower overall failure rate but a higher rate of severe capsular contracture and worse esthetic results. On the other hand, irradiation of tissue expander and subsequent replacement with definitive implant presents a greater risk of reconstructive failure, but a lower rate of severe capsular contracture and a more favorable esthetic result.

Regarding other less used techniques such as TRAM flap and LDF, the literature lacks studies comparing the superiority between autologous techniques, however, they agree that both techniques are reliable, safe and reproducible when there is a need to perform PMRT[8,10,14,16].

CONCLUSION

Despite the well-known importance of radiotherapy in the context of oncological indications for breast cancer, its impact on the various techniques and strategies for breast reconstruction in women undergoing mastectomy is undeniable. We found studies suggesting potential benefits for each technique used in breast reconstruction in patients with an indication for PMRT, suggesting specific and varying measures to reduce the occurrence of potential complications. In this review, we did not find enough scientific evidence to determine the best technique and the best sequencing for this purpose. Radiotherapy and Chemotherapy together significantly increase the rate of complications associated with breast reconstruction techniques. Moreover, in the double-phase reconstruction strategy with tissue expander along with PMRT, the timing of irradiation (before or after the exchange of the expander with the definitive implant) interferes with the overall failure rate of breast reconstruction, as well as other surgical complications.

In conclusion, the choice of the surgical technique and the timing of radiotherapy should be defined by the surgeon and the

Table 1. Characteristics of studies.

Author, year	Study Type	Approach	n	AT	Results	Conclusion
Ogita et al., 2018[1]	Retrospective	To evaluate PMRT complication rates for tissue expanders versus permanent implant.	81	32	Total reconstruction failure, reoperation and infection rates were 12.3, 13.6 and 11.1%, with 5-year cumulative of 16.7, 16.6 and 12.2%, respectively.	There were no significant differences in complication rates concerning the timing of radiotherapy. Age over 55 years is a risk factor for complications.
Cordeiro et al., 2015[3]	Retrospective	Comparative study of results related to reconstructive failure, aesthetic results and capsular contracture in patients undergoing PMRT with expanders and implants.	1,790	108	6-year failure rates higher in patients with expanders (32% versus 16.4%; $p < 0.01$). Patients undergoing PMRT with expanders had a higher proportion of very good to excellent esthetic results (75% versus 67.6%; $p < 0.01$) and lower rates of grade IV capsular contracture ($p < 0.01$).	The overall risk of reconstructive failure is significantly higher for patients with tissue expander irradiation compared to patients with definitive implant irradiation. Esthetic results and capsular contracture rates are slightly better when the tissue expander is irradiated.
Chuba et al., 2017[4]	Retrospective	Investigation of previous risk factors in implant and tissue expander surgeries with PMRT.	127	120	Complications were: Grade 0 (no complications; 43.9%), Grade 1 (tightening and/or implant deviation or Grade II Baker capsular contracture; 30.9%), Grade 2 (infection, hypertrophic scar or incisional necrosis; 9.8%), Grade 3 (Baker grade III capsular contracture, wound dehiscence or imminent implant exposure; 5.7%), Grade 4 (implant failure, implant exchange or Baker grade IV capsular contracture; 9.8%). Considering non-irradiated breasts, there were two cases (1.6%) of Grade 3/4 complications. Patients with depression were more likely to experience Grade 3 or 4 complications (29.4% versus 13.2%; $p = 0.01$).	Higher rates of reconstruction complications are expected in patients receiving radiotherapy. History of depression was significantly related to increase in complication rates.
Lam et al., 2018[7]	Retrospective, cohort	Analysis of complications including prosthesis loss, seroma and infection in patients undergoing chemotherapy and PMRT. Esthetic results assessed using a four-point scale.	452	144	The overall postoperative loss of prosthesis was 2.7%, 5.3% for patients undergoing adjuvant chemotherapy, increasing to 11.3% in patients receiving both chemotherapy and radiotherapy. Chemotherapy and radiotherapy independently were the main statistically significant risk factors for expander or implant loss [incidence rate ratio, 13.85 ($p = 0.012$) and 2.23 ($p = 0.027$), respectively]. Implant loss for patients undergoing chemotherapy combined with radiotherapy was also significant [incidence rate ratio, 4.791 ($p<0.001$)].	PMRT doubles the risk of prosthesis loss compared to adjuvant chemotherapy, but it is an acceptable option after breast reconstruction with immediate two-stage prosthesis in a multidisciplinary environment.

Continue...

Table 1. Continuation.

Author, year	Study Type	Approach	n	AT	Results	Conclusion
Lee et al., 2016[8]	Retrospective	Analysis of outcomes and survival of patients with stage II or III breast CA who underwent modified radical mastectomy and chemotherapy followed by PMRT.	492	11-191	The 5- and 10-year disease-free survival rates were 81% and 76% for the TRAM flap group and 78% and 73% for the non-flap group. The 5- and 10-year overall survival rates were 89% and 73% for the TRAM flap group and 83% and 74% for the non-flap group.	No statistically significant difference in rates of local recurrence, distant metastasis, disease-free survival and overall survival when comparing immediate TRAM flap reconstruction with surgeries without reconstruction.
Carrabin et al., 2015[10]	Retrospective, case-control	Analysis of esthetic outcomes of patients operated with the LDF technique undergoing PMRT.	87	78	The result of cosmetic reconstruction was rated as good or very good in 86% of the cases, with the consistency of the irradiated breast rated as good or very good in 93% of the cases. Complementary fat transfer was performed on average 11 months after radiotherapy in 58% of cases.	The LDF technique has good tolerance for PMRT.
Chen et al., 2016[14]	Retrospective	Analysis of complications in patients undergoing immediate breast reconstruction with expander implants in the context of radiotherapy.	76	72	The probability of developing complications in patients in the RXT-pre and RXT-post groups were 2.0 and 2.3, respectively.	For patients who received pre-mastectomy total breast radiotherapy, autologous augmentation is strongly recommended. The sub-analysis of the pre-RXT group showed a significantly higher mean number of total complications
Chiasson et al., 2020[16]	Retrospective	Review of the use of the LD flap in conjunction with prosthetic devices, regardless of the need for adjuvant radiation, to determine the safety and effectiveness of this approach as a primary reconstruction method.	201	-	There was no difference between non-irradiated and irradiated patients, except for reconstructive loss, which was 3.6% in the non-irradiated group and 16.6% in the irradiated group ($p = 0.03$). However, one third of irradiated patients had reconstructive loss for reasons unrelated to radiotherapy.	The immediate reconstruction with LDF in conjunction with prosthetic devices is a reliable and safe option, even in the context of adjuvant radiotherapy, as autologous tissue attenuates many radiotherapy injuries.

LDF: latissimus dorsi flap; PMRT: Post-mastectomy radiotherapy; post-RXT: external beam radiotherapy performed after surgery; pre-RXT: external beam radiotherapy performed before surgery; TE: Tissue expander; TRAM: Rectus abdominis flap. AT: average time (months)

multidisciplinary team of each service in a shared decision with the patient, emphasizing that depending on the choice, we may have a higher overall failure rate in the reconstruction, but on the other hand, the quality of the final esthetic results could be better. This review acknowledges the need for further prospective randomized comparative studies between the different techniques and strategies for breast reconstruction in patients who are candidate for mastectomy and breast reconstruction and with an indication for PMRT, so as to build better scientific evidence to support decision-making.

AUTHORS' CONTRIBUTION

M.L.O.A.B.: writing – revision & editing, investigation, project administration, supervision, writing – original draft. M.A.A.B.O.: writing – revision & editing, investigation, project administration, supervision, writing – original draft. C.C.P.A.: writing – review & editing, investigation, project administration, supervision, writing – original draft. C.Ê.M.L: writing – revision & editing, formal analysis, investigation, project administration, supervision, writing – original draft.

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CASE REPORT
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Pleomorphic adenoma of the breast

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ABSTRACT

Pleomorphic adenoma (PA) is a common tumor of the salivary gland, but rarely occurs in the breast. PA of the breast is a benign tumor that usually presents as a periareolar nodule. Core-needle biopsies may yield misdiagnosis with complex fibroadenoma, phyllodes tumor and metaplastic breast cancer due to the mixture of stromal and epithelial elements. We present a case of PA of the breast suspected after core-needle biopsy, but confirmed after surgical excision. The importance to make a correct diagnosis consists in avoid extensive unnecessary surgery, such as mastectomy, since PA can be treated with local surgical resection.

KEYWORDS: adenoma, pleomorphic; breast neoplasms; neoplasms, glandular and epithelial.

INTRODUCTION

Pleomorphic adenoma (PA) is a benign tumor commonly found in the parotid gland, but rarely described in breasts[1]. PA is a mixed tumor, composed of epithelial and myoepithelial elements, which can occur in either breast or parotid tissues due to its common embryological ectodermal origin[2]. Accurate identification is important to avoid misdiagnosis such as a primary sarcoma, an adenomyoepithelioma, a Phyllodes tumor or metaplastic breast carcinoma that may lead to unnecessary extensive surgery[3-5]. Thus, we report a case of a PA suspected after core needle biopsy and confirmed after surgical excision.

CASE REPORT

An asymptomatic 71-year-old woman presented a lump in her right breast during breast cancer screening. Mammography and breast ultrasound showed a periareolar, irregular and hypoechoic lump in the lower internal quadrant of the right breast, measuring 9 mm (Figure 1). Core-needle biopsy demonstrated a benign biphasic neoplasm, composed of a mixture of epithelial and myoepithelial cells, with a focus of apocrine metaplasia, sclerosing adenosis, and chondromyxoid stroma (Figure 2). Immunohistochemistry revealed p63 and calponin expression in myoepithelial cells, in addition to a low Ki67 proliferation index (Figure 2). Based on histopathological findings, it was not possible to differentiate between complex fibroadenoma and PA of the breast. Consequently, the patient underwent surgical excision of the nodule. Examination of the surgical specimen showed a well-defined lesion with clear margins, and characteristic epithelial and myoepithelial elements without atypia, embedded into a chondromyxoid stroma, with foci of chondroid metaplasia (Figure 3). Final pathological report confirmed PA of the breast.

This study was approved by the Ethics and Research Committee of the A.C. Camargo Cancer Center (number 4.213.207) and was conducted following the Helsinki Declaration principles. All information and images were de-identified.

DISCUSSION

PA of the breast was first reported in 1906[6]. Since then, less than a hundred cases have been reported worldwide, including one from Brazil[3,7-12]. PA typically occurs in females between 23 to 85 years of age[7] and is usually located in the periareolar region and in the right breast[13]. PA presents clinically as a breast nodule with an average size of 2 cm, which can be palpable and difficult to differentiate from breast cancer[11,14].

There are no specific imaging findings of PA[11]. Although PA is often reported as a well-circumscribed lump, it may demonstrate irregular contours on breast ultrasound and can appear as a lump without microcalcifications on mammography[3]. On pathological examination, PA appears as a circumscribed lesion that is clearly demarcated from the surrounding tissue, and is characterized by a mixture of epithelial and mesenchymal components such as glandular ducts, myoepithelial cells, myxomatous stroma, and cartilaginous

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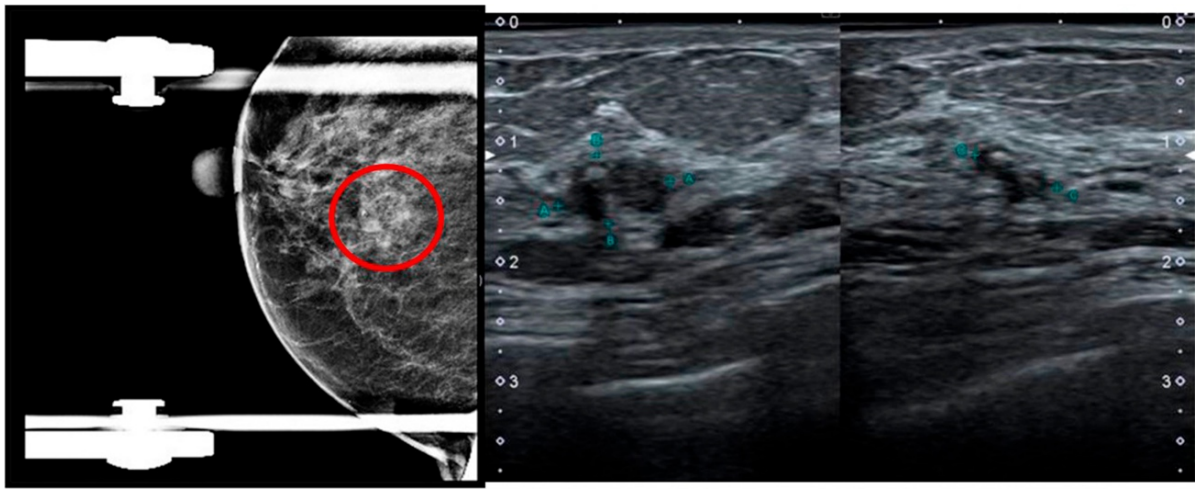

Figure 1. Mammography (left) and ultrasound (right) demonstrating a 9 mm hypoechoic and irregular nodule in the lower internal quadrant of the right breast.

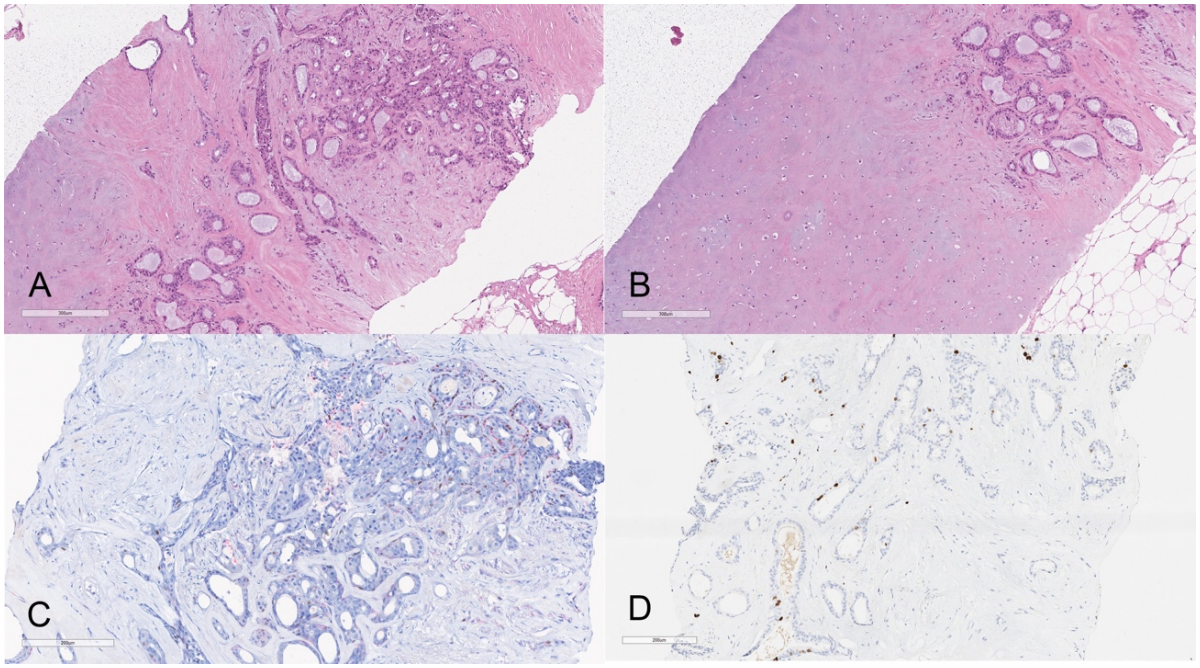

Figure 2. Hematoxylin-eosin stain (100x) of core-needle biopsy specimen of (A) the right breast lump showing glands surrounded by epithelial and myoepithelial cells and (B) focus of chondromyxoid stroma. Immunohistochemical (100x) of core-needle biopsy specimen of the right breast lump showing positivity for p63 (nuclear) and (C) calponin (cytoplasmatic) expression in myoepithelial cells and (D) low Ki67 proliferation rate.

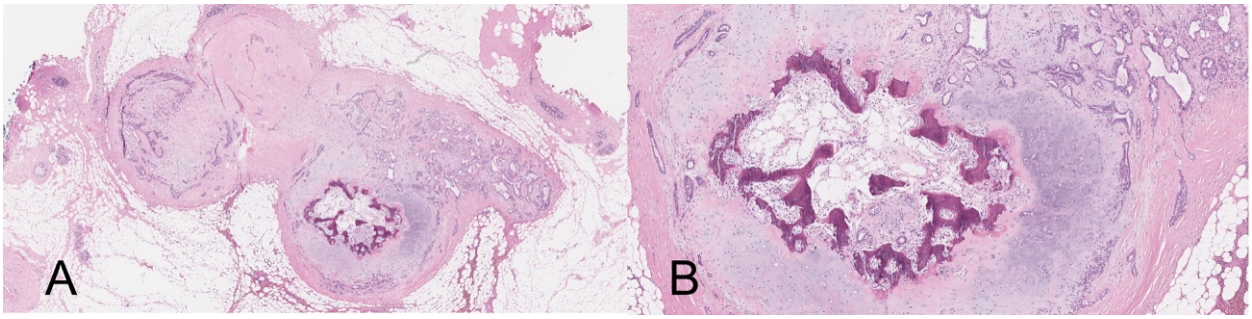

Figure 3. (A) Hematoxylin-eosin stain of surgical specimen showing a well-defined lesion under low-power magnification (40x) and (B) a high-power magnification (200x) of pleomorphic adenoma with glandular elements in chondromyxoid stroma with cartilaginous and osseous metaplasia.

components. PA diagnosis can be difficult in core biopsy specimens because it must be differentiated from complex fibroadenoma or phyllodes tumor[1,3,4,15]. In addition, two case reports have described misdiagnoses of breast PA identified as matrix-producing metaplastic breast cancer in core-needle biopsy specimens[4,15].

Recommended treatment is local resection with 3 mm of clear margins to avoid disruption of the tumor capsule[2,4]. PA is an indolent tumor, but recurrences have been reported[2,13]. Recurrence is usually in the adjacent subareolar area, with an average postoperative recurrence interval of 4 years[2,4].

CONCLUSIONS

Breast PA is a rare tumor that presents clinically as a periareolar nodule. Despite its being a benign tumor, the diagnosis from core-needle biopsy specimens is difficult due to the mixture of stromal and epithelial elements that can raise a differential diagnosis of complex fibroadenoma, phyllodes tumor, and metaplastic breast cancer. This case illustrates a presentation of a breast lump in an elderly patient for whom breast cancer was the primary diagnostic consideration. Diagnostic accuracy is essential to avoid extensive surgical overtreatment such as mastectomy, as PA can be cured by local surgical resection.

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AUTHORS' CONTRIBUTIONS

M.S.: Conceptualization, Project administration, Writing — original draft, Writing — review & editing.
G.T.L.F.: Writing — original draft.
T.A.D.: Writing — original draft, Writing — review & editing.
V.F.C.: Writing — original draft, Writing — review & editing.
S.M.T.C.: Writing — review & editing.
C.A.B.T.O.: Writing — review & editing,
F.B.A.M.: Supervision, Writing — review & editing.

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CASE REPORT
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Minimally invasive treatment of gynecomastia by ultrasound-guided vacuum-assisted excision: report of a case series

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ABSTRACT

Introduction: Gynecomastia (GM) is a benign proliferation of glandular breast tissue in men. Some cases need surgical intervention. Traditional open surgery by semicircular inferior periareolar incision is the most common surgical approach. In order to obtain better esthetic results, some alternatives to open surgery have been proposed, such as liposuction, endoscopic mastectomy, and vacuum-assisted excision (VAE). **Objective:** To describe the technical surgical approach of ultrasound-guided VAE of GM and its results from a case series. **Method:** This is an evaluation of seven GM cases submitted to ultrasound-guided VAE with a 10G needle using the ENCOR® BD whole circumference automated breast biopsy system in Redimasto – Redimama, a Brazilian breast center. The result was considered good or satisfactory when it showed minimal remaining gland, good symmetry, no retraction, necrosis, hypertrophic scar, or displacement of the nipple-areola complex. All patients answered a questionnaire to evaluate their satisfaction and perception of the procedure. **Results:** Seven (7) patients with Simon grade 1 and 2 bilateral GM underwent ultrasound-guided VAE. No case of displacement, necrosis, or retraction of the nipple-areola complex, post-procedure bleeding, infection, skin necrosis, or asymmetry was detected. No patient reported decrease or change in nipple sensation or erection. All patients had bruises and hematomas that spontaneously resolved within 30 days. All results were considered good or excellent by patients and surgeons. **Conclusion:** Minimally invasive ultrasound-guided VAE is an excellent alternative for the treatment of GM. It is better indicated for Simon grade 1 and 2 GM, with good and excellent esthetic results, small scar, and low rates of nipple and areolar complications. It allows an outpatient procedure with low morbidity (local anesthesia) and fast recovery.

KEYWORDS: gynecomastia; mammary ultrasonography; interventional ultrasound; needle bipsy.

INTRODUCTION

Gynecomastia (GM) is a benign proliferation of glandular breast tissue in men[1]. It is the most common male breast disorder, accounting for nearly 60% of them. It can be unilateral or, most often, bilateral. GM is a common condition with a prevalence of 32% to 65%, depending on age, and can affect up to 70% of all pubescent boys[2]. A man's lifespan has three peaks: the first occurs during infancy, the second during puberty, and the third in middle-aged and older men[1,2]. GM in infancy and puberty resolves spontaneously in most cases. Proper investigation is highly recommended among adults and older adults to exclude underlying diseases[1].

GM typically results from an absolute or relative deficiency of androgen action or excessive estrogen action in the breast tissue[2]. No treatment is necessary for asymptomatic adolescents or men, but it is required when GM is progressive, painful, or causes cosmetic discomfort. It usually resolves by itself or by removing the underlying cause, such as medication, anabolic-androgenic steroid abuse, or treatment of systemic diseases[3]. Medical therapy can also be prescribed for patients with a recent diagnosis — within two years —, but is less effective for long-standing GM. Some cases need surgical intervention. According to Simon, GM can be classified into grades[4] (Table 1).

Traditional open surgery by semicircular inferior periareolar incision is the most common surgical approach, but it may cause

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significant morbidities, such as asymmetry, poor scarring, and nipple-areola complex retraction or necrosis[5-7]. In order to obtain better esthetic results, some alternatives to open surgery have been proposed, such as liposuction, endoscopic mastectomy, and vacuum-assisted excision (VAE)[7-9].

In the last few years, the use of vacuum-assisted devices, originally created to diagnose breast lesions by radiologically-guided procedures, has shown to be promising in the surgical management of GM[8-12].

OBJECTIVE

To describe the technical surgical approach of ultrasound-guided VAE of GM and its results from a case series.

METHOD

The study consists of seven GM cases evaluated from December 1, 2018, to December 1, 2019. The patients underwent ultrasound-guided VAE with a 10G needle using the ENCOR® BD whole circumference automated breast biopsy system in Redimasto — Redimama, a Brazilian breast center. Before the procedure, all patients were submitted to a clinical evaluation with full history and physical examination by a breast surgeon, as well as mammography, breast ultrasound, and blood tests. All patients signed an informed consent form for the VAE procedure. All procedures were performed by breast surgeons experts in ultrasound-guided VAE. The procedures took place in the breast center, in an outpatient approach, through a 3 mm incision in each breast, with local anesthesia, using 2% lidocaine and bupivacaine when necessary, according to the maximum dose for the patient's weight. No sedation was necessary. After the 10G needle was introduced and positioned via ultrasound, the automated vacuum device was activated (Figures 1 and 2). The number of fragments extracted from each breast varied according to the surgeon's judgment of each case, taking into account the amount of breast tissue during clinical examination, mammography, and breast ultrasound before surgery, as well as the real-time breast ultrasound evaluation during the procedure. The vacuum method for dense breasts with fine precision was used for all cases. The resection performed left a 1-cm thick gland behind the nipple, just like the standard surgical procedure. At the end of the VAE of the GM, vacuum and manual suction of the residual cavity were performed to avoid or reduce the incidence of postoperative hematomas and bruises. Only one patient had the surgical cavity marked with a metal clip. Mammographic images were obtained one and six months after VAE to evaluate the removal of the glandular tissue (Figure 3). Patients wore a thoracic compression belt for at least 30 days. Follow-up was scheduled at 7 days, 14 days, 1 month, 2 months, and 6 months after the procedure, and consisted of clinical examination, pictures, and survey of the patient's and breast surgeon's satisfaction. The result was considered good or satisfactory when it showed minimal remaining gland, good symmetry, no retraction, necrosis, hypertrophic scar, or displacement of the nipple-areola complex. All patients answered a questionnaire to evaluate their satisfaction and perception of the procedure.

Table 1. Simon grade of gynecomastia.

Grade 1	small breast without excess skin
Grade 2	moderate breast without excess skin
Grade 3	moderate breast with excess skin
Grade 4	large breast with excess skin

Figure 1. Ultrasound-guided vacuum-assisted excision of gynecomastia: surgical approach.

RESULTS

Seven patients with Simon grade 1 and 2 bilateral GM underwent ultrasound-guided VAE. One of them had undergone previous traditional open surgical treatment of GM with unsatisfactory results, and all patients expressed their wish to have an excision with less morbidity, small scars, and good esthetic outcome. The mean age was 27.5 years (ranging from 19 to 34 years). The average procedure time was 28 minutes (ranging from 23 to 54 minutes). The main complaint and indication for the procedure was the esthetic appearance of GM, followed by physical deformity. One patient had an areola fissure caused by the vacuum suction during the procedure, which was promptly sutured and did not affect the final esthetic result. At follow-up, all patients and breast surgeons reported excellent or good satisfaction (Figures 4 and 5), and at the six-month review, no patient presented recurrence or asked for another intervention or open surgery. No patient had postoperative seroma, bleeding, or hemorrhage or needed to be taken to the operating room at any time, during or after the surgical procedure and follow-up. All procedures were performed in an outpatient setting, with local anesthesia and no sedation. Histological evaluation revealed benign GM in all patients. No case of displacement, necrosis, or

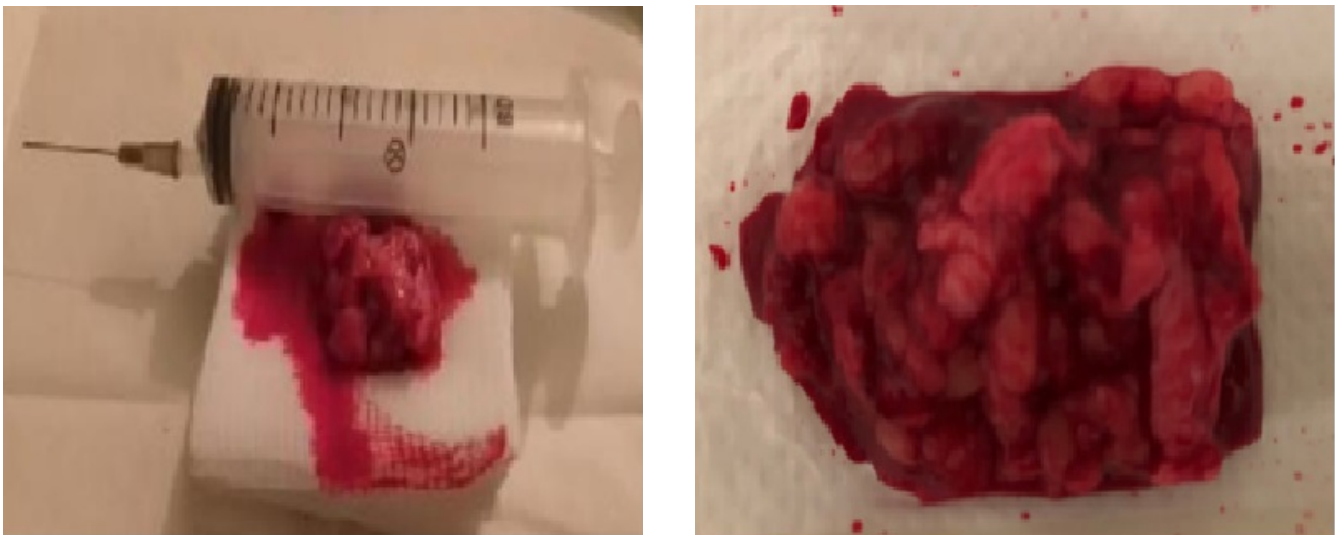

Figure 2. Ultrasound-guided vacuum-assisted excision of gynecomastia: surgical specimen.

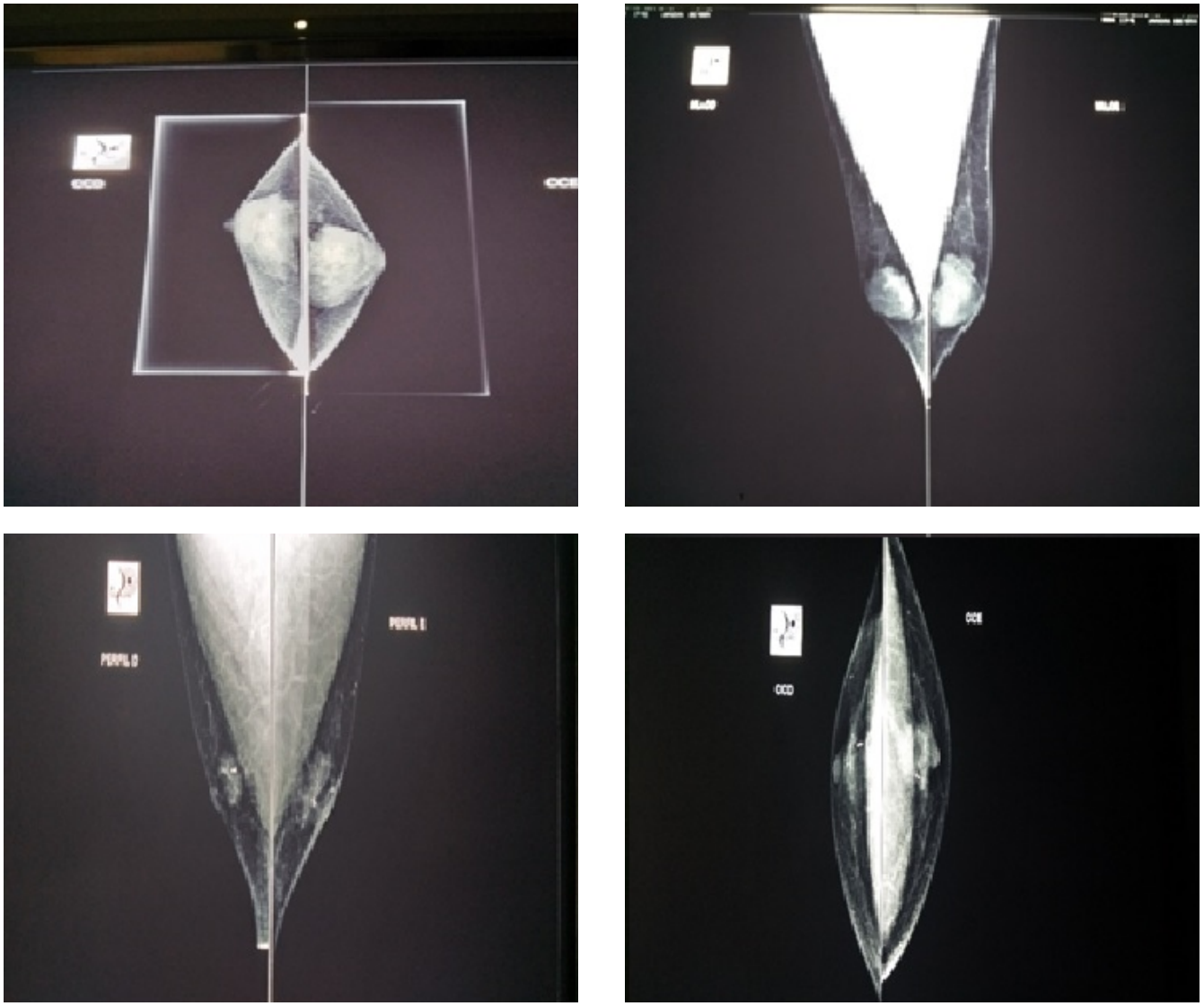

Figure 3. Mammograms before and six months after ultrasound-guided vacuum-assisted excision of gynecomastia.

retraction of the nipple-areola complex was detected. None of the individuals investigated presented postoperative bleeding, infection, skin necrosis, or asymmetry. No patient reported decrease or change in nipple sensation or erection. All patients had bruises and hematomas that spontaneously resolved within 30 days of VAE, with excellent or good cosmetic results and no skin sequelae. The individuals investigated were able to return to their life activities in 2 days and to physical work in 14 days. Physical activities were allowed two weeks after the procedure. All results were considered good or excellent by patients and surgeons (Table 2[13] and Figure 3).

DISCUSSION

The main goal of treating GM is to remove the excess of breast tissue, achieving the best symmetry with minimal scarring and good or excellent esthetic results. Different from subcutaneous mastectomy for cancer treatment, the purpose of GM surgery is not to excise all breast tissue in an oncologic fashion. GM surgery aims to remove enough breast tissue to obtain a good cosmetic result and avoid clinical recurrence. The open surgical approach is still the standard procedure for persistent GM after one or two years, especially when associated with psychological distress, unsatisfactory body image, and avoidance of activities in which the chest is exposed (sports and swimming)[4]. For years, subcutaneous mastectomy through a semicircular inferior areolar incision, associated or not with liposuction, has been the gold-standard surgical procedure for this condition. The results are usually satisfactory, but postoperative complications are common, including areola deformity or retraction; "saucer-shaped defect" (from over-resection of breast tissue); seroma; poor scarring, such as retraction, hypertrophic scar, or keloid formation; wound dehiscence; and nipple retraction, necrosis, or altered sensation. The side effects of standard surgery have been a long-standing concern. In 1987, Courtiss et al. published an article reporting that 101 out of 159 patients presented high complication rates after traditional excision for the treatment of GM, including under-resection (21.9%), "saucer-shaped defect" (18.7%), poor scarring (18.7%), hematoma (16.1%), and seroma (9.4%)[6]. In order to decrease morbidity and improve esthetic results, the GM treatment should improve with new surgical techniques and minimally invasive procedures.

More recently, some groups have described an endoscope-assisted subcutaneous mastectomy[5], with a smaller incision. However, this technique did not eliminate the potential complication of having a scar on a visible part of the chest or axillae, and the risk of nipple-areola complex complications remains[8].

In 2010, the Royal College of Surgeons of England published the first article about a vacuum-assisted biopsy device associated with liposuction to provide a minimally invasive approach for GM, with excellent results[8]. The group suggested that ultrasound guidance could be positive in those cases. One year later, the Chinese experience with a vacuum-assisted biopsy device was also published[9]. Recently, the indications

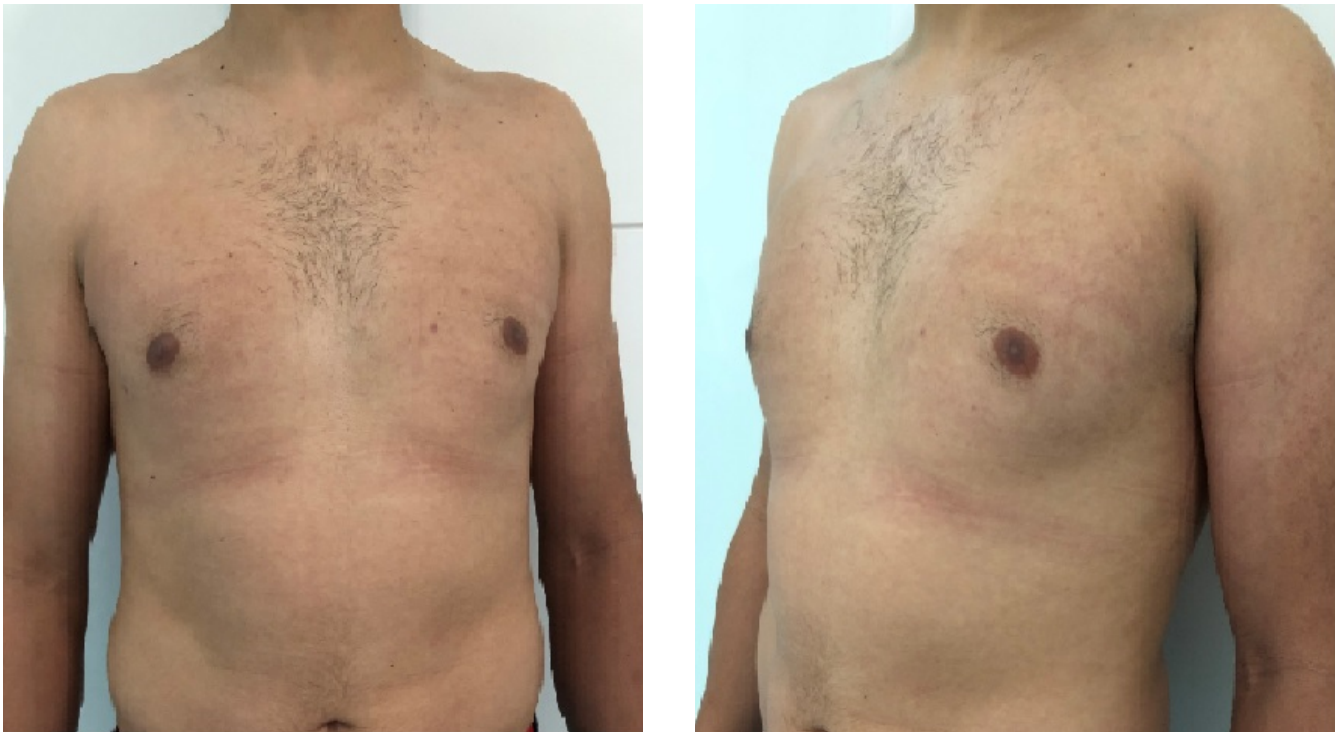

Figure 4. 34-year-old man with Simon grade 2 gynecomastia.

for VAE have expanded to more severe Simon grades of GM, with the procedure performed in the operating room under general anesthesia[10].

A recent prospective series compared VAE of GM with open traditional surgery. The VAE group had significantly smaller scar sizes (0.40 ± 0.08 cm vs. 5.34 ± 0.38 cm, $p < 0.01$), shorter healing time (3.67 ± 0.71 days vs. 7.90 ± 0.92 days, $p < 0.01$) and hospitalization (2.60 ± 0.62 vs. 7.17 ± 0.83 days, $p < 0.01$), as well as higher postoperative satisfaction (4.70 ± 0.60 scores vs. 3.20 ± 0.55 scores, $p < 0.01$). The incidence rate of bruises was significantly higher in the VAE group compared to the open surgical group (47% vs. 17%, $p = 0.013$ and 54% vs. 20%, $p = 0.007$), respectively[11].

The benefits of VAE are similar to those of minimally invasive procedures in general — reduced morbidity, better esthetic results, fewer recovery days, and no hospitalization time or cost[8]. The results from this series corroborate the findings of other series and studies. Depending on the GM grade, the VAE can be performed with local anesthesia, with or without sedation. With the evolution of vacuum-assisted devices, better vacuum aspiration, and multiple fragments collected in an automated circular approach with one-step needle insertion, it is possible to remove a considerable amount of breast tissue in a few minutes, reducing the odds of infection or complication. A study reported a median time of 50

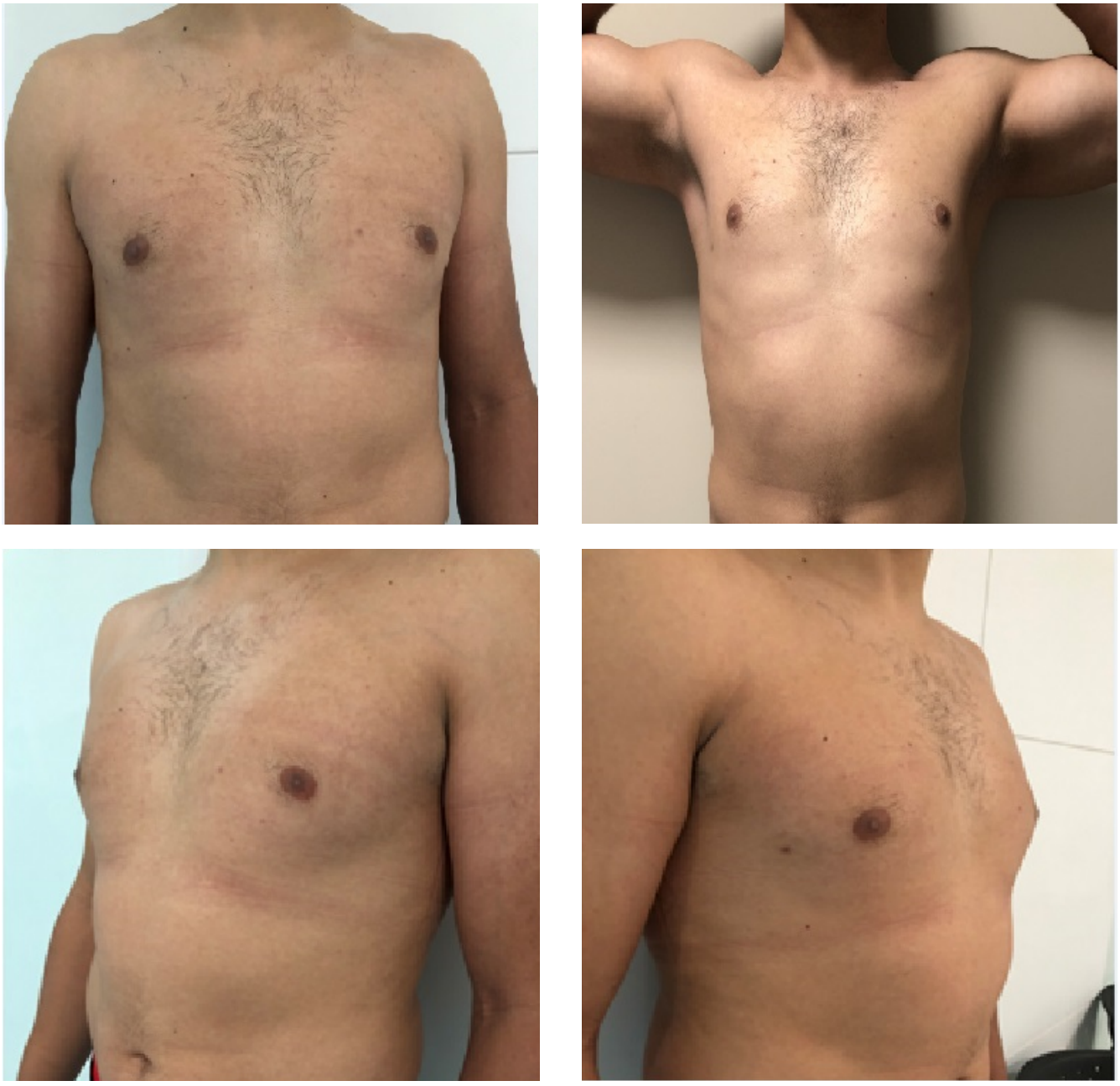

Figure 5. Same patient six months after ultrasound-guided vacuum-assisted excision of gynecomastia.

Table 2. Satisfaction evaluation: adaptation of the consultation satisfaction questionnaire.

n = 7	Esthetic discomfort	Physical deformity	Medical indication	
Patient complaint	5	2	0	
n = 7	Excellent	Good	Regular	Bad
Final esthetic result (6 months) – patient	5	2	0	0
Final esthetic result (6 months) – surgeon	4	3	0	0
n = 7	yes	no		
Would the patient repeat or recommend the procedure for someone?	7	0		
Was the procedure well tolerated?	7	0		
Complications n = 7				
Seroma	0			
Bruises	7			
Anesthesia scar	0			
Bleeding	0			
Areola fissure	1			
Displacement, necrosis, or retraction of the nipple-areola complex.	0			
Decrease or change in nipple sensation or erection	0			

Source: Mazzarone[13].

minutes using an 8G needle with a semi-automated device[8], while in this series, the median time was 25 minutes using a 10G needle with a whole circumference automated device. The patients' procedure tolerance was high, even with just local anesthesia. Automated devices allow faster, safe, and outpatient procedures that preclude hospitalization and have the potential of saving costs.

Doubts related to long-time recurrence remain and require more studies for clarification. Longer follow-up will be necessary to evaluate this issue better. Nevertheless, the amount of breast tissue excised described by the literature and this series is not different from the traditional open surgical specimen. Mammographic images gradually change over time. After six months, it is possible to estimate the amount of tissue resected, but, like in benign surgeries, the degree of architectural distortion is high, especially due to large hematomas and bruises, which fade with time. This finding indicates that the best moment for a mammographic evaluation of the amount of breast resected should probably be after one year of the procedure.

CONCLUSION

Minimally invasive ultrasound-guided VAE is an excellent alternative for the treatment of GM. It is better indicated for Simon grade 1 and 2 GM, with good and excellent esthetic results and low rates of nipple and areolar complications. It allows an outpatient procedure with low morbidity (local anesthesia) and fast recovery. Hematomas and bruises are always present due to the nature of the approach. Breast surgeons can obtain satisfactory cosmetic results with little morbidity and postoperative complications, such as nipple retraction or necrosis. Ultrasound-guided VAE has become a valuable approach for the surgical management of Simon grade 1 and 2 GM, with or without liposuction according to necessity. Trials comparing VAE of GM with open surgery should also evaluate clinically relevant recurrence throughout the years to establish the safety of these surgical approaches over time.

AUTHORS' CONTRIBUTION

C.V.: Investigation, Methodology, Project Administration, Writing — Review and Editing.
H.L.: Investigation, Methodology, Project Administration, Supervision, Validation, Writing — Review and Editing.
T.O.: Writing — Review and Editing, Formal Analysis.
P.B.: Methodology, Writing — Review and Editing.
S.F.: Data Curation, Validation, Writing — Review and Editing.
O.J.: Investigation, Visualization, Writing — Original Draft, Validation.

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CASE REPORT
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Silicone granuloma mimicking lymphatic metastases in a patient with breast cancer

Márcia Marinho[1*], Luís Castro[2], Maria José Rocha[2], Arlindo Ferreira[2]

ABSTRACT

Silicone breast implants are commonly used, even for reconstruction after mastectomy in malignant disease. In this setting, the presence of suspicious lymphadenopathy should be investigated, because it could represent disease progression. A case of a woman with left breast cancer (more than 20 years ago) and prosthesic reconstruction is reported. She developed a second breast cancer on the opposite side. During follow up, a suspicious lymphadenopathy was seen in the computed tomography scan, but the final diagnosis corresponded to a siliconoma. Silicone granuloma is a difficult diagnosis in these cases, but must be considered.

KEYWORDS: breast implants; adverse effects; breast neoplasm; surgery; granuloma; diagnostic imaging; woman.

INTRODUCTION

Silicone breast implants are commonly used for breast augmentation and also in reconstruction procedures, including those after mastectomy for oncologic purposes[1].

Leakage from either ruptured or intact implants can occur, stimulating granulomatous foreign body reaction. The resulting silicone granuloma, also known as siliconoma, corresponds to the inflammatory response to the free liquid silicone but could be misinterpreted as a malignant situation[2-4].

Siliconomas can occur locally (manifesting as lymphadenopathy) or present at distant sites (rare cases in lower limbs and vulva have been already described) because the silicone polymer is a lipid soluble and therefore its migration in fatty tissue can easily take place[5,6].

In patients with breast cancer submitted to reconstruction with silicone implants after mastectomy, the presence of siliconomas could mimic a progression of the disease. Careful evaluation is needed and the differential diagnosis must take into consideration this benign pathology.

CASE REPORT

A 66-year-old female patient with a previous left mastectomy in 1995 for neuroendocrine carcinoma (T2N0M0) was now referred to our institution for abnormal mammography of the right breast.

The neuroendocrine carcinoma was treated with chemotherapy and hormone therapy with tamoxifen. A breast reconstruction with silicone implant on the left side and a symmetrizing surgery on the right breast were performed.

In 2012, corrective surgery was done due to fibrous encapsulation of the implant.

In February 2018, the patient was referred for polymorphic microcalcifications in the upper external periareolar region of the right breast causing a dystrophic aspect on the mammogram. These alterations were not present in the previous exams.

On clinical examination, no alterations in inspection nor solid mass were palpable in both breasts. The ultrasound showed no abnormalities.

A stereotactic biopsy was performed and the histological exam revealed ductal carcinoma in situ (DCIS), nuclear grade 2 with >90% of estrogen receptors positivity. A tumorectomy was conducted with the neoplasia adjacent to the lower surgical margin and one millimeter (mm) apart from the medial one. The microcalcifications were present in the histological exam.

The case, pTis (DCIS) Nx, was discussed by a multidisciplinary team and it was decided to proceed with radiotherapy (RT) and hormone therapy.

In the planning computed tomography (CT) scan prior to the RT session, a suspicious lymphadenopathy of the internal mammary

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lymph nodes was identified (Figure 1). To confirm the findings, a CT scan with contrast was performed and showed an apparent intact silicone implant, as well as lymph nodes in both internal mammary chains (Figure 2), with 15 mm maximum diameter on the left side.

A core needle biopsy was performed (Figure 3) and the histological exam revealed "vacuolated histiocytes with little birefringent material in polarized light and multinucleated giant cells with vacuoles of different sizes and asteroid bodies; compatible with silicone granuloma".

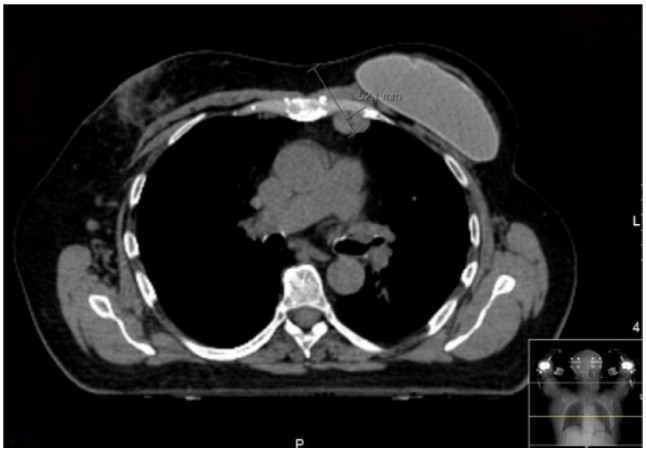

Figure 1. Planning computed tomography scan prior to radiotherapy (coronal plan): lymphadenopathy of the internal mammary lymph nodes on the left side.

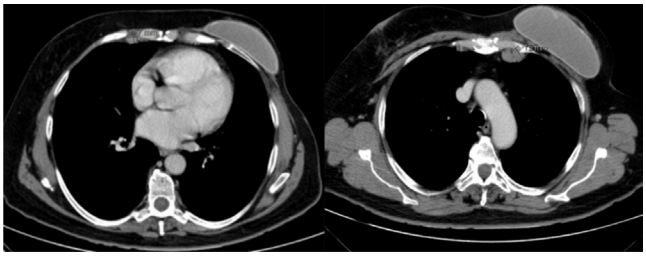

Figure 2. Contrast computed tomography scan (coronal plan): lymph nodes in both internal mammary chains, the biggest one on the left side with 15 mm.

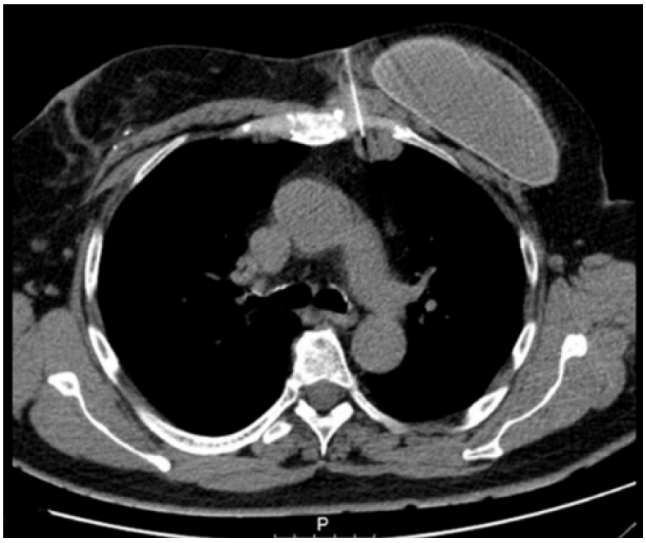

Figure 3. Core needle biopsy of the suspicious lymphadenopathy.

The patient underwent successful RT treatment. Currently, under hormone therapy, the patient is being followed up (two years) without complications.

The presence of suspicious lymph nodes in a breast cancer case could change the staging and consequently, the strategic therapy. In a patient with silicone breast implants, silicon granulomas must be considered in the differential diagnosis of suspicious lymphadenopathy.

DISCUSSION

Silicone granulomas are benign lesions that could have a similar presentation to malignancy.

In patients with breast cancer and silicone implants, the presence of lymphadenopathy might not always correspond to a progression of the disease, but instead to a siliconoma. Therefore, clinicians must be aware of this condition and consider it in the differential diagnosis[3,6].

Silicone material could migrate even without clear evidence of implant rupture. The migration mechanism is still unknown, but it has been suggested that absorbed silicone molecules may follow vascular spread or travel with lymphatic flow[5].

Magnetic resonance imaging (MRI) findings could include evidence of implant collapse and also free silicone particles outside the prosthetic shell[7]. Sonographic evaluation may reveal echogenic lesions with a "snowstorm" appearance, but there are no specific findings. Positron emission/ computed tomography (PET CT) in patients with siliconomas may be falsely positive[7].

Pathological tissue specimens remain the gold standard for diagnosis of siliconomas. Histological findings include foamy macrophages and refractile droplets of clear material[7].

In conclusion, silicone granulomas are benign lesions rarely reported in the literature, which could nonetheless occur in patients with silicone implants, either for breast augmentation or reconstruction in oncologic patients. These lesions could be easily misinterpreted as a malignancy progression in breast cancer patients with silicone implants. Although this pathology demands a high grade of suspicion, clinicians should consider it in the differential diagnosis for proper staging and treatment of oncologic patients.

AUTHORS' CONTRIBUTIONS

M.M.: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, writing – review & editing.
L.C.: data curation, visualization, validation, review & editing.
M.J.R.: visualization, validation.
A.F.: visualization, validation.

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CASE REPORT
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VRAM flap for locally advanced breast cancer

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ABSTRACT

The authors presented a case of a patient with locally advanced breast cancer, with mammary and axillary localization, initially considered non-resectable, with good response after neoadjuvant chemotherapy. Due to the location of the lesion and the need for extensive resection, radical mastectomy was performed, associated with reconstruction with myocutaneous flap of the vertical rectus abdominis muscle. Different therapeutic options, the reasons that determine this choice, and local long-term control were discussed.

KEYWORDS: breast neoplasms; myocutaneous flap; surgical flaps; neoadjuvant therapy.

INTRODUCTION

Vertical Rectus Abdominis Myocutaneous (VRAM) is a versatile flap[1], generally used in pelvic reconstruction[2] and, to a lesser extent, in the reconstruction of the chest wall after extensive resection in locally advanced breast carcinoma. It has a lower rate of necrosis compared to the Transverse Actus Abdominal Muscle Flap (TRAM), but it is associated with the presence of visible abdominal incision[1,3], with a small cosmetic input[4].

In the case of reconstruction of defects after mastectomy in locally advanced tumors, with the need to use myocutaneous flaps, the latissimus dorsi flap is the option[5]. However, there is space for the use of the abdominal external oblique muscle flap[6], TRAM or VRAM[7]. A case in which VRAM was used was presented here, along with a discussion on the factors related to its choice and results.

CASE REPORT

A 63-year-old patient was admitted with a palpable complaint in her right breast six months ago. Upon examination, an ulcerated tumor mass with a foul odor was noted, measuring 15 × 13 cm, occupying external quadrants of the right breast, with extension to the axillary and dorsal regions (Figure 1A). In the right axillary region, lymph node conglomerate adhered to deep planes, cT4b cN2 M0, was palpated. Core biopsy was performed with anatomopathological (AP) analysis, identifying invasive ductal carcinoma, histological grade 3. Immunohistochemical study found a triple negative tumor. The patient underwent neoadjuvant chemotherapy (AC-T), with disappearance of ulceration, stability of the mammary lesion and satellite skin lesions, compromising the axillary and dorsal regions (Figures 1B and 1C). Subsequently, surgical treatment was performed using the Madden modified radical mastectomy technique (Figure 1D) with rotation of VRAM to close the defect in the chest wall (Figure 2), with good postoperative evolution (Figure 3). The AP analysis of the surgical specimen found metaplasic infiltrative carcinoma of the adenosquamous type, histological grade 3, measuring 8 cm in the longest axis, with cutaneous involvement, free surgical margins and 0/12 axillary lymph nodes compromised by neoplasia. Adjuvance was performed with radiotherapy (plastron + axilla + supraclavicular fossa – 28 X 180 cGY). During the follow-up, 14 months after the end of treatment, the disease progressed with distant disease (lung) and, later, bone and plastron. Local recurrence (plastron) and death occurred at 37 months and 44 months after surgical treatment, respectively.

DISCUSSION

In choosing the flap to close the defect after mastectomy, several factors were involved: the surgeon's experience, the size of the defect, training in microsurgical techniques, and the potential complications involved. In general, the microsurgical and

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myocutaneous flaps allow the closure of areas superior to the fasciocutaneous or dermo-fat flaps, except for the ipsilateral thoracoabdominal dermofat (ITADE) flap, which, despite covering an extensive area, is associated with a higher rate of complication and cutaneous necrosis, being the necrosis greater than 4.3% and smaller than 34.7%[6,8,9].

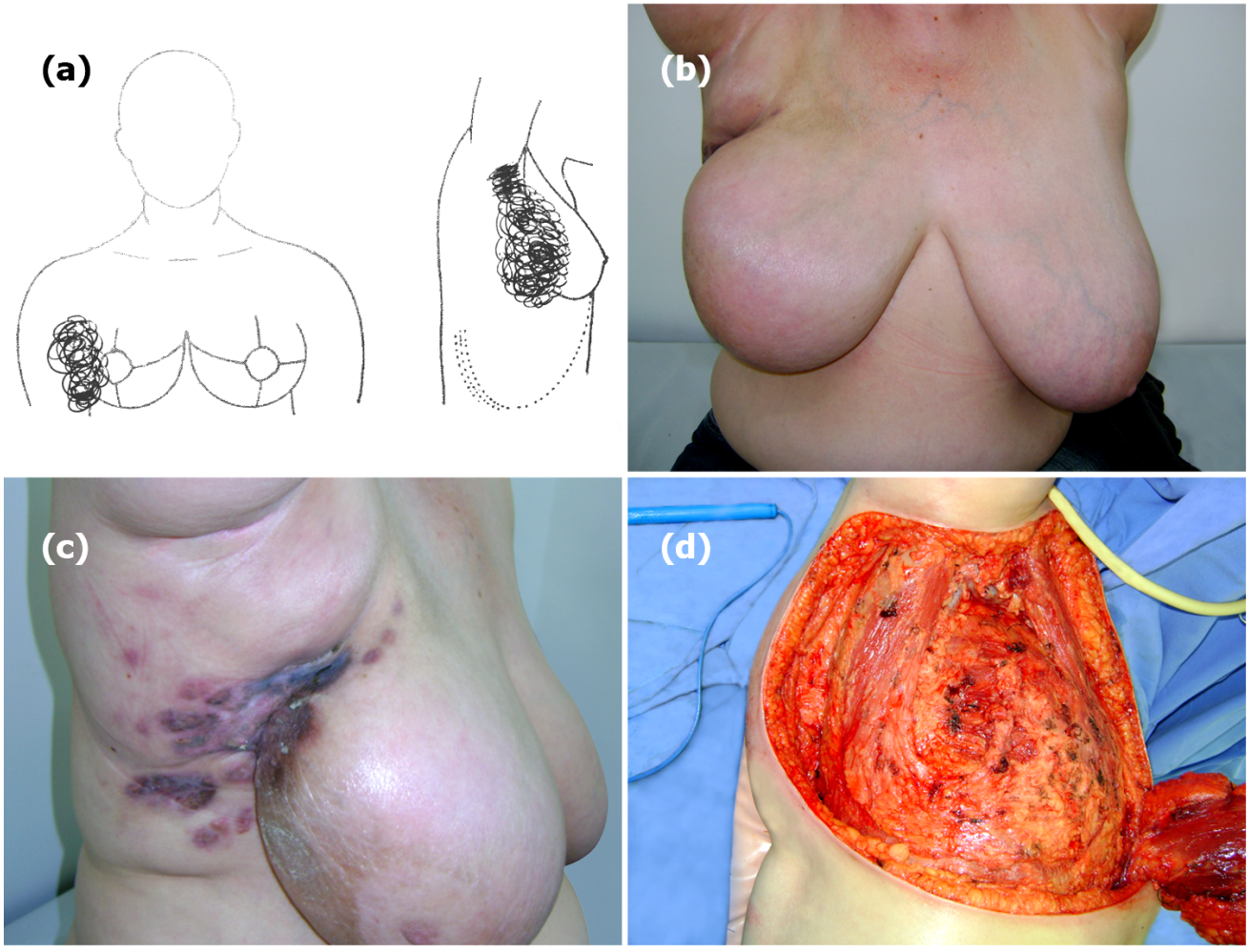

Figure 1. (A) Schematic representation prior to treatment; (B) control after neoadjuvant chemotherapy; (C) resection area; (D) resected area.

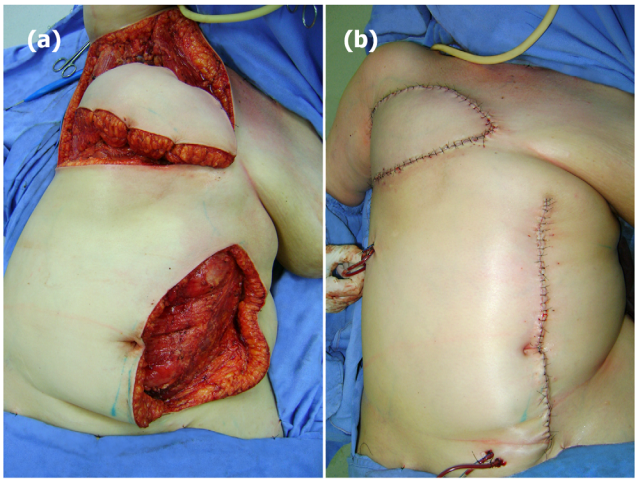

Figure 2. Vertical rectus abdominis flap. (A) Fabrication of the flap and transposition to the axillary region. Observe the use of zone I of the flap only. (B) Surgical result.

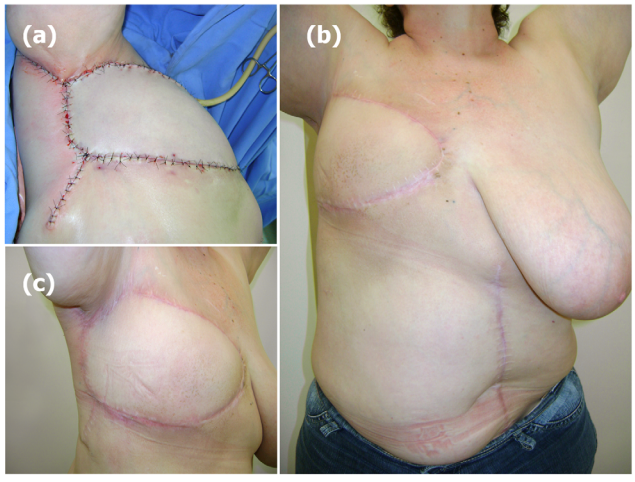

Figure 3. Vertical rectus abdominis flap: flap coverage area, with local healing and final result. (A) Intra-operative; (B and C) postoperative.

It is known that few services have professionals qualified in microsurgical techniques, and the breast surgeon must have knowledge of the different reconstruction possibilities and their strengths and weaknesses, allowing the best choice of the myocutaneous flaps to be used. The latissimus dorsal flap is the one of choice. Despite disadvantages such as the incision on the back and the limitation of the skin donor area for very extensive defects[5], it is the flap with a low rate of surgical complication and greater ease of execution.

The flap of the oblique abdominal muscle, little found in the literature, does not determine important fragility of the abdominal wall and is associated with an extensive scar, although it has a higher necrosis rate (less than 10%)[10]. The modification of the myocutaneous flap of the abdominal oblique, despite allowing coverage of an upper area, is associated with a high rate of necrosis (70.6%)[6], representing a good option for use in extreme cases.

VRAM, in turn, is a versatile flap, associated with a low rate of complications, but it generates fragility in the abdominal wall, as well as the presence of a vertical scar[7,11], with less necrosis compared to TRAM[12].

In the present case, the reconstruction was performed by mastologists and oncologic surgeons with knowledge of different flaps. The tumor was found in the breast and in the lateral region of the chest, which influenced the choice of the flap. The resection of an extensive lateral chest area, determined by tumor involvement, reduced the donor area of the latissimus dorsi, limiting the choice of this flap. Thus, the contralateral rectus abdominis muscle was considered as a choice, facilitated by the patient's body mass index and the availability of adipose tissue. In its manufacture, only the irrigation zone I[3] was used, with a good donor area for coverage. In extreme cases, however, the skin donor area can be enlarged, with increased flap size and greater coverage, using tissue from zones II and III[13].

The patient evolved well, and the surgery associated with the reconstruction allowed local control of the disease for 37 months, which positively influenced the quality of life[2].

CONCLUSION

VRAM is an excellent flap that allows coverage of large skin defects in the chest wall. It constitutes yet another option to be considered after resection of locally advanced breast tumors.

AUTHORS' CONTRIBUTION

R.A.C.V: Conceptualization, formal analysis, investigation, methodology, project administration, supervision, writing — original draft, writing — review & editing.
R.L.H.: Conceptualization, formal analysis, writing — review & editing.
L.I.B.: Data curation, writing — review & editing.
I.O.-J.: Investigation, methodology, supervision, writing — original draft, writing — review & editing.

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CASE REPORT
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Myeloid sarcoma in the breast in a patient with acute myeloid leukemia: a case report

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ABSTRACT

Myeloid sarcoma infiltration into the breast of patients with acute myeloid leukemia is rare. The present study reports the case of a 56-year-old woman diagnosed with AML and an incidental finding of a breast tumor. The nodule biopsy raised the suspicion of invasive lobular carcinoma and poorly differentiated angiosarcoma. Subsequent immunohistochemical study concluded the diagnosis of myeloid sarcoma. The varied image presentations, the lack of knowledge of clinical data and complementary propaedeutics, and the histopathological similarity with certain primary breast lesions make it difficult to discover secondary infiltration by myeloid sarcoma in this unusual site.

KEYWORDS: breast neoplasms; sarcoma, myeloid; leukemia.

INTRODUCTION

Myeloid sarcoma (MS) is the tumor form of acute myeloid leukemia (AML), consisting of a collection of myeloid blasts in an anatomical site other than the bone marrow. It is addressed by several names, including myeloblastoma, monocytic sarcoma and chloroma. Other synonyms are granulocytic sarcoma and extramedullary myeloid tumor[1]. Although it can affect any region of the body, its presentation in the breast is extremely uncommon, having been, until 2005, only 67 cases recorded in the literature[2], with additional episodes reported sporadically until recently[3]. Skin, lymph nodes, gastrointestinal tract, bone, soft tissues and testicles are the most frequent sites of involvement[4]. MS can be found isolated in about a quarter of cases, or during the course of AML, chronic myeloid leukemia, myelodysplastic syndrome or other myeloproliferative disorders[3]. MS occurs with an incidence of 2% to 14% in AML[5]. The age of onset varies from 29 to 72 years, mean age of 42 years[1]. It is difficult to define typical characteristics of the affected patients, so the diagnosis can only be confirmed through pathological examination with immunohistochemistry.

CASE REPORT

A 56-year-old female patient presented at the emergency unit complaining of adynamia, moderate dyspnea, hyporexia, and weight loss within the past two months, with symptomatic worsening in the last 15 days. She carried recent tests that revealed significant anemia, thrombocytopenia, and leukocytosis, and was admitted to our institution for investigation. On physical examination, she was pale, sarcopenic, dehydrated, and had multiple lymph node enlargements. She was diagnosed with AML subtype M4, using bone marrow aspirate, and induction chemotherapy with cytarabine was started six days after admission.

Chest tomography performed to assess respiratory distress revealed an incidental finding of a nodule in the right breast and axillary lymph node enlargement. Mammography (Figure 1) revealed a nodule in the right breast measuring 2 cm, located at the junction of the lateral quadrants, oval, with indistinct margins, being categorized as a suspected lesion of malignancy. Complementary ultrasonography (Figure 2) confirmed the suspicious findings, identifying an oval nodule parallel to the skin, circumscribed, heterogeneous, with slight posterior acoustic reinforcement, without flow to the color Doppler study, at the union of the lateral quadrants on the right, at 9 o'clock, 4 cm from the papilla, and measuring 2 × 1.4 × 1.8 cm. A thick needle biopsy revealed breast tissue infiltrated by round, diseased cells, with a high nucleus-cytoplasm ratio. In the absence of clinical and laboratory information, and due to the probabilities, the hypotheses of invasive lobular carcinoma and poorly differentiated angiosarcoma were raised. However, an immunohistochemical

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study ruled out these hypotheses by revealing a negative result for cytokeratins 7 and AE1/AE2.

The patient's clinical weakness postponed the surgical approach to breast injury, which was followed up with imaging tests until conditions favored invasive treatment. A new mammogram (Figure 3), performed seven months following the first, after three complete chemotherapy cycles, no longer showed the nodule, which on ultrasound showed a significant reduction in tumor mass. Leukemic infiltration in the breast became the main clinical suspicion, considering the behavior of the tumor in the face of chemotherapy directed at leukemia and the inconsistent diagnoses between anatomopathological and immunohistochemical studies.

Nine months after the diagnosis, the patient underwent an open excisional biopsy, and the examination of the surgical specimen showed sparse foci of remaining neoplasia. A new immunohistochemical study, in the light of clinical information, resulted in positive tumor cells for the CD34, CD45, lysozyme, CD15, and myeloperoxidase markers. Thus, the diagnosis of breast infiltration by MS was confirmed. Ten months after diagnosis, and after four cycles of chemotherapy, the patient died as a result of complications from the underlying disease.

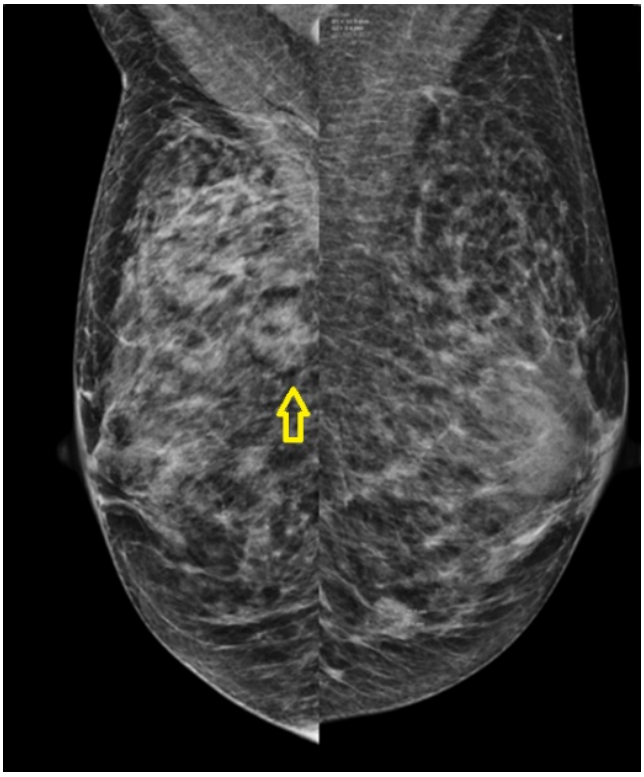

Figure 1. Mammography in oblique mediolateral view showing a nodule in the right breast, measuring 2 cm, at the junction of the lateral quadrants, oval, with indistinct margins (BI-RADS 4A).

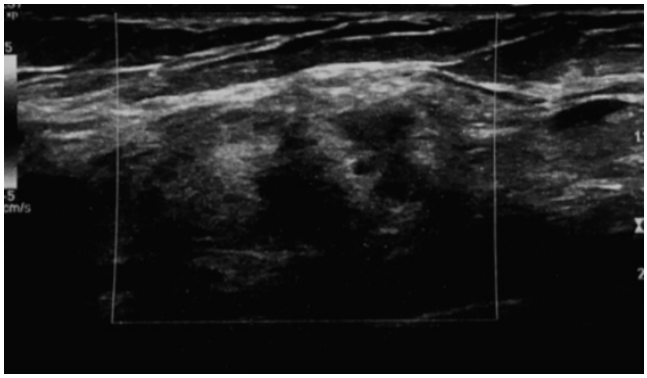

Figure 2. Ultrasonography showing an oval nodule, parallel to the skin, circumscribed, heterogeneous, without flow to the color Doppler study, at the union of the lateral quadrants, at 9 am, 4 cm apart from the papilla, measuring 2 × 1.4 × 1.8 cm.

DISCUSSION

MS can occur in three clinical contexts: simultaneously with blood and bone marrow involvement, as in the case of our patient; as isolated recurrence of AML; and prior to the manifestations of systemic leukemia[6]. Even in patients with bone marrow invasion, breast MS is quite uncommon. Patients with breast MS have mainly a painless mass, without inversion or nipple secretion[7]. In the case studied, the patient did not present evident symptoms. However, previous studies report both asymptomatic presentation and presentation of painful palpable nodulation[7]. Therefore,

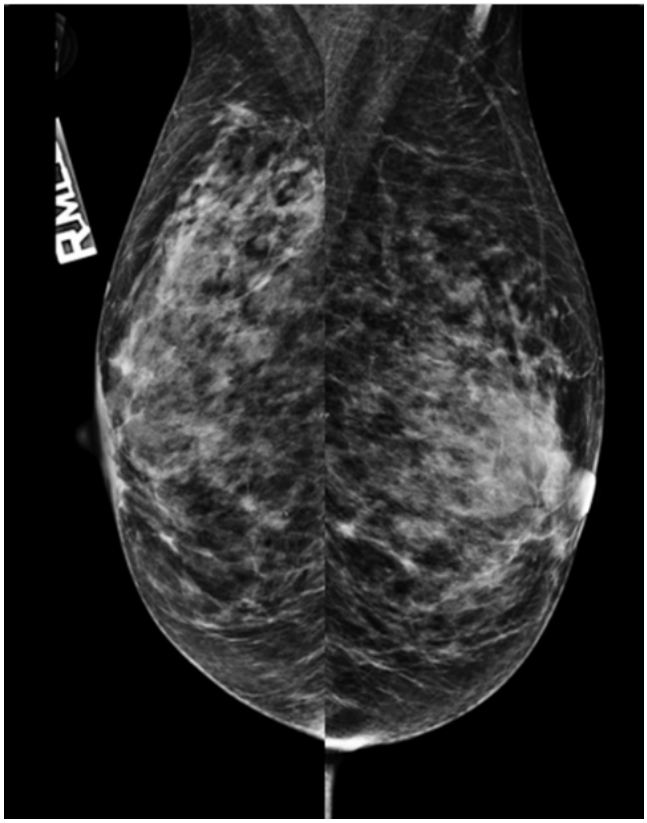

Figure 3. Mammography performed after 3 cycles of chemotherapy no longer demonstrated the nodule.

it is difficult to define typical clinical presentations of the tumor. The morphological, imaging, and histological characteristics are as variable as the clinical presentation, of difficult diagnosis, especially if it is of low suspicion. Mammography shows that breast leukemias have three mammographic patterns: breast masses, architectural distortions, and no abnormalities. Most breast masses are hyperdense, have a rounded shape and microlobulated margins, and occasionally accompany internal microcalcifications. On ultrasound, they usually present as solitary or multiple masses that tend to be homogeneously hypoechoic with microlobulated or indistinct margins[2]. The immunohistochemical study is extremely useful in recognizing MS, the most specific markers of myeloid differentiation being myeloperoxidase and lysozyme, both positive in this case. The levels of myeloperoxidase positive cell expression in MS tend to be between 66 and 83.6%[6]. The most common differential diagnoses include invasive lobular carcinoma, non-Hodgkin's lymphoma or even non-neoplastic conditions, such as inflammation and extramedullary hematopoiesis[8]. In the reported case, the diagnosis of invasive lobular carcinoma was the first to be considered.

The treatment modalities recorded in the literature include surgical excision, radiotherapy, and chemotherapy and depend on the patient's clinical conditions, the size of the tumor, and the systemic response. However, most studies have concluded that all patients with MS should receive mastectomy or breast sectorectomy combined with standard systemic chemotherapy, and overall survival appears to be longer in patients treated with chemotherapy compared to those who do not receive it. Although the patient in the case presented has died, due to previous clinical weakness, it is important to note that the response of the breast tumor to chemotherapy was quite significant, since it was no longer identified in the follow-up mammography and had a significant reduction demonstrated on ultrasound.

CONCLUSION

The case presented here shows the importance of the clinical-pathological correlation and maintenance of high diagnostic suspicion for MS in patients with AML, although morphological or histological characteristics suggest other conditions. In the case of the presented patient, the diagnosis of AML helped to consider the diagnostic possibility of MS and, consequently, contributed to a satisfactory mammary tumor regression. The rarity of breast involvement by this type of tumor means that most of the information available on its behavior and its manifestations is obtained from case reports and small retrospective studies. Its extremely variable presentation makes diagnosis difficult through imaging exams, requiring the use of all the resources necessary for anatomopathological and immunohistochemical diagnosis.

AUTHORS' CONTRIBUTION

A.L.K.O.: conceptualization, investigation, methodology, project administration, supervision, validation.
J.H.M.A.: methodology, research, writing – original draft, writing – review & editing).
J.H.A.S.: writing – review & editing, validation.
J.M.O.: writing – review & editing.

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CASE REPORT
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Adenoid cystic carcinoma of the breast: case report

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ABSTRACT

Adenoid cystic carcinoma (AdCC) of the breast is an uncommon invasive lobular neoplasm whose morphology is similar to the homonymous tumor of salivary glands and with a peculiar behavior toward the "triple-negative" (TN) profile. Tumors belonging to this family do not immunohistochemically express three of the main prognostic biomarkers and tend to show a more aggressive behavior. However, this rare histological pattern of breast cancer is generally associated with good prognosis. In this study, the authors describe the case of a 49-year-old woman diagnosed with this rare malignant tumor and who underwent breast-conserving surgery. Recent studies have aimed to understand the genes, genetic alterations, and etiological aspects related to the still obscure etiopathogenesis of AdCC. Thus, morphological and molecular aspects relevant to AdCC and reported in the literature will be discussed.

KEYWORDS: adenoid cystic carcinoma; breast neoplasms; triple-negative breast neoplasms.

INTRODUCTION

Currently, breast cancer stands out in prevalence among women, associated with increasing longevity, new lifestyle habits, and early menopause[1]. Accurate anatomopathological diagnosis of tumors is essential to adopt an adequate and effective therapeutic approach, enabling satisfactory patients' survival[1,2]. Among the different histological types of breast cancer, adenoid cystic carcinoma (AdCC) stands out for being uncommon and presenting peculiar morphological and immunohistochemical characteristics, which provide a paradoxically favorable prognosis[2]. Due to the rare incidence, many cases of AdCC are not properly recognized or recorded in epidemiological databases, hindering the elucidation of AdCC etiopathogenic correlations[2,3]. In a recent publication on breast neoplasms, the World Health Organization (WHO) histologically subclassifies AdCC into classic, solid-basaloid, or with high-grade transformation[2]. These definitions are essentially based on architectural, cytological, and immunohistochemical characteristics, but they can also be objectified by genomic profiling[2,4,5]. Genomic studies performed by *in situ* hybridization (FISH) or by polymerase chain reaction (PCR) have gained prominence in the characterization and understanding of the AdCC etiopathogenesis[4]. The present case report addresses the diagnosis of an uncommon malignant breast tumor compatible with classic AdCC of the breast after histological and immunohistochemical evaluation.

CASE REPORT

A 49-year-old woman sought a mastology service due to the presence of a mass in the left breast. Despite apparently normal nipples and breasts, absence of bulging or skin retraction, a medium-radiodensity nodule with partially defined contours was observed at 2 o'clock in the left upper lateral quadrant, measuring 1.1 cm (Figure 1A). As no suspicious microcalcifications and alterations in the lymph nodes of the left axillary region were evidenced, it was classified as BI-RADS 0. According to ultrasonography exam, there was a lesion suggestive of a BI-RADS 4 solid nodule, described as a nodular image, solid, rounded, hypoechoic, heterogeneous, with regular contours, with no flow capture on Doppler, 30 mm from the nipple, 12.8 mm from the skin, and measuring 9.6 x 8.1 mm (Figures 1B and 1C). All identified lymph nodes were echographically normal.

For anatomopathological analysis, core biopsy products and a sectionectomy surgical specimen of the upper lateral quadrant of the left breast were obtained, in addition to a biopsy of the patient's sentinel lymph node. According to macroscopic inspection, the tumor was a white nodule, measuring 2.5 cm, located deep to the breast (Figure 1D), whereas the lymph nodes, sentinel or non-sentinel, were soft to the cut with light-brown color and approximate size of 1.0 cm. Histological analysis showed a neoplasm consisting of epithelial cells in a tubular and cribriform pattern, with few solid elements [score 1], similarly to the salivary gland tumor, diffusely infiltrating the breast parenchyma and adipose tissue. In addition, round and elongated

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cells with moderate nuclear atypia [score 2], low mitotic index [score 1] as well as substance in the gland lumens (sometimes basophilic, sometimes eosinophilic) were verified. In special Alcian Blue staining, myxoid materials were observed in the basal lamina and gland content, confirming mucopolysaccharide composition (Figure 2).

The immunohistochemical study showed negativity for estrogen, progesterone, and HER2 receptors, dual cell population, epithelial and myoepithelial, as well as positivity for Ki-67 and CD117 (c-KIT) (Table 1).

Considering all the characteristics of the neoplasm, the following diagnosis was concluded: adenoid cystic carcinoma of the breast, with the following pathological staging: *pT2pN0pMX*. Taking into account the known favorable prognosis of this carcinoma and the absence of metastases, the propaedeutic and curative approach of sectionectomy dispensed with chemotherapy or radiotherapy. Furthermore, regular mastology follow-up was adopted with the patient for active surveillance of tumor recurrence.

DISCUSSION

Adenoid cystic carcinoma of the breast (AdCC), a rare and important variant of invasive carcinoma, is worthy of attention of pathologists who routinely deal with breast biopsies[6,7]. Ghabach et al. estimated an age-adjusted incidence rate of 0.92 for every 1 million people/year, predominantly verified in postmenopausal women with a median age of 60 years[8]. This epidemiological finding is corroborated by studies showing an incidence rate ranging between 0.1% and 3.5% among all breast carcinomas and age ranging between 33 and 74 years[2,4,6,8,9]. With a histological aspect resembling the homonymous tumor of salivary glands, in the breast, for classic types of AdCC, it requires a differential diagnosis with collagenous spherulosis, intraductal carcinoma with cribriform pattern[5,6,10]. As for the solid variant of AdCC, it requires differentiating it from neuroendocrine carcinoma, solid papillary carcinoma, metaplastic carcinoma, and malignant lymphoma[4,6,9,11]. Although the etiopathogenic relationship has not yet been confirmed, some authors suggest an association of

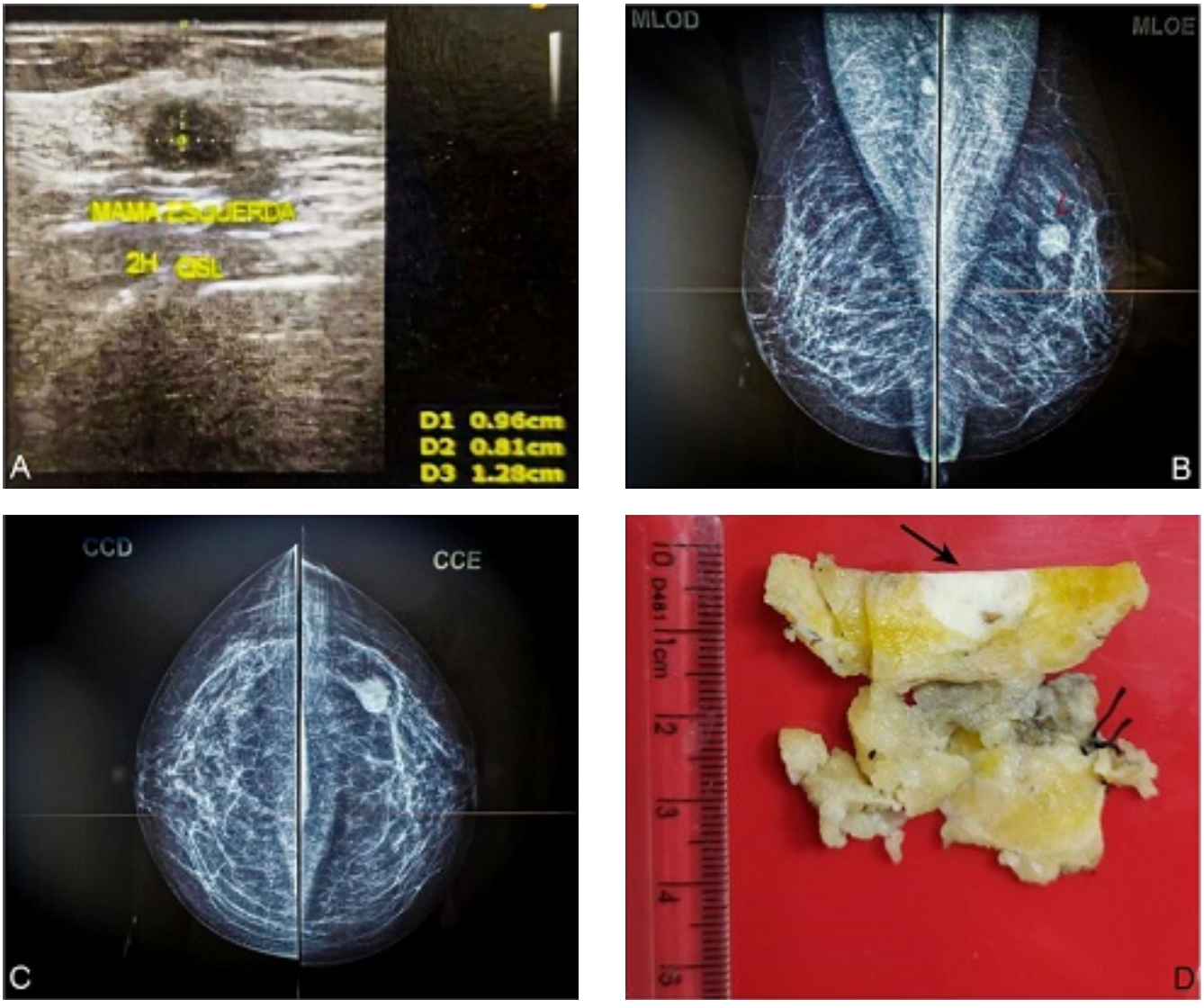

Figure 1. Macroscopic aspects of adenoid cystic carcinoma of the breast in imaging and anatomopathological tests.

AdCC with benign lesions such as microglandular adenosis, tubular adenosis, adenomyoepithelioma and fibroadenoma[2,4,5,12].

The tumor is histologically composed of a dual cell population (epithelial and myoepithelial), with a triple-negative molecular profile for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)[2,4,7,13]. Furthermore, it presents basophilic secretions, formed by materials from the basal membrane, in the pseudoglandular lumens, which are better observed in the special Alcian Blue or PAS (Periodic acid-reactive Schiff) stains[2,8,9,12]. Other findings that support the AdCC hypothesis are potential immunohistochemical markers, such as CD117 and Ki-67, as well as the evaluation of MYB-NIFB gene fusion or mutated genes BRAF, FGFR1/2, ERBB2, and NOTCH1, through molecular cytogenetic techniques as PCR or FISH[2,4,6,9,12].

Among these mutations, the activation of NOTCH1, simultaneously considered oncogene and tumor suppressor gene, is identified in solid and triple-negative (TN) tumors, such as AdCC, influencing resistance to chemotherapy drugs[2,14]. *In vitro* and *in vivo* studies performed by Stoeck et al. showed that, unlike NOTCH2 and HES4 biomarkers, the increasing expression of NOTCH1 induces sensitivity to the gamma-secretase inhibitor MRK-003, as monotherapy or combined with the antineoplastic drug Paclitaxel[14] The transcription product of this mutated gene is significantly

Table 1. Immunohistochemical profile of the tumor based on the sectionectomy product.

Antibody	Clone	Result (neoplastic cells, %)
Estrogen Receptor	ER1	Negative (0)
Progesterone Receptor	PgR636	Negative (0)
HER2 oncogene product	SP3	Negative (score 0)
Ki-67: Cell proliferation antigen	MIB1	Positive (15)
Calponin (muscle and myoepithelial cells)	Calp	Focally positive
Tumor Protein p63 (squamous/ transitional epithelium; myoepithelial cells)	DAK-p63	Positive (myoepithelial cells)
CD117 – KIT gene product	YR145	Positive

KIT: Proto-Oncogene Receptor Tyrosine Kinase; HER2: Human epidermal growth factor receptor 2.

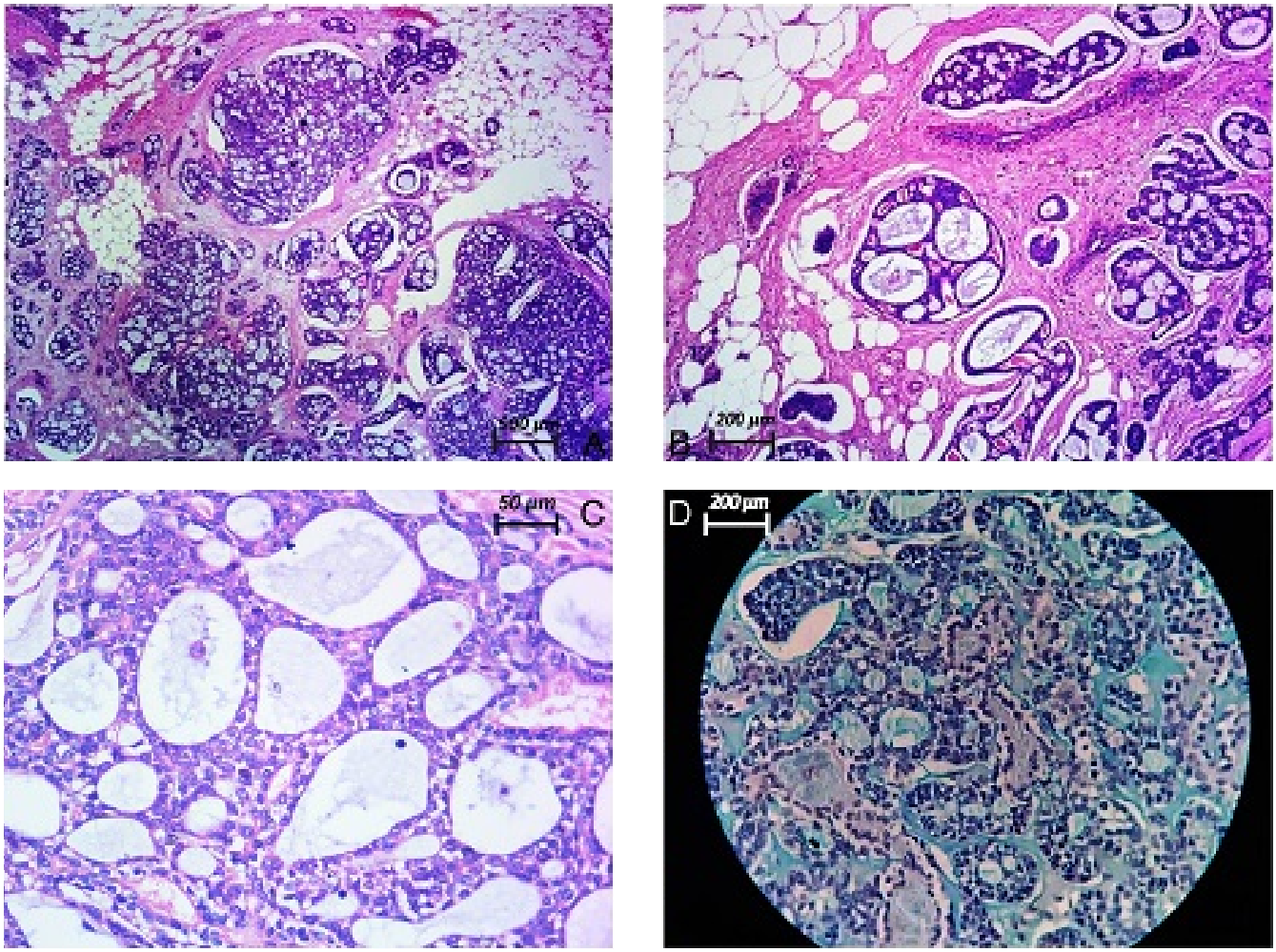

Figure 2. Microscopic aspects of adenoid cystic carcinoma of the breast.

higher in basal-like and mesenchymal TN tumors[13,14]. These basal-like tumors are subclassified into types 1 and 2, according to genetic expression, influencing sensitivity to chemotherapeutics[14,15]. Despite sharing morphological characteristics with solid-basaloid AdCC, the differential diagnosis is enabled by investigating the tumor extension and identifying typical areas of AdCC[2].

On mammography, the lesion, whose size varies between 1 and 140 mm, is observed as a lobulated or irregular mass, sometimes cystic, which may have defined borders; on ultrasound, it is solid and hypoechoic, or a heterogeneous mass[6,9,16]. According to guidelines from the American Society of Clinical Oncology/College of American Pathologists, breast tumors suspected of malignancy should be biopsied by core biopsy for immunohistochemical evaluation[7]. The expression or absence of markers is able to predict biological behavior and therapeutic response[7,13,17]. Among them, positivity for PR and ER favorably correlates with prognosis and hormonal therapeutic effect[13], unlike HER2, which is usually associated with aggressiveness and hormonal resistance[7,17].

Belonging to the family of tumors with TN immunophenotype, the combination of the absence of expression of endocrine receptors (ER and PR) and HER2 results in a favorable prognosis for patients with breast AdCC[2,8,18]. In the last decade, studies concluded that the neoplasm is well-located, especially in the retroareolar region, with a high survival rate of approximately 95% in 10 years and, in tumors measuring less than 14 mm, there is no lymph node involvement[2,16]. Although uncommon, there are records of cases reporting axillary lymph node involvement, metastases to lungs, bones, livers, brain, and kidneys[2,8,16], mainly observed in AdCCs with high-grade transformation, in which the glandular histological pattern is essentially replaced with a solid area, a subtype with worse prognosis[2,4,9,12,18].

Breast AdCC is not restricted to the female population; there are epidemiological studies that show this rare neoplasm in men[2,18]. A retrospective analysis of 19 cases of AdCC treated at a Canadian hospital reported involvement in a 53-year-old man, with a tumor measuring 4.0 cm, lymph node involvement, and presence of metastasis[18].

Although TN tumors have a clinical profile related to worse prognosis and resistance to hormonal therapy and trastuzumab, AdCC has an essentially favorable prognosis and can be conservatively treated[2,14,15,18]. To date, there is no consensus on the ideal treatment for AdCC[8,10]. Based on the characteristics of the tumor and the patient's immunological conditions, breast-conserving surgery, mastectomy, chemotherapy, or radiotherapy are indicated[2,10]. This adjuvant modality is prioritized when lymph node dissemination is detected[10,16,18]. In situations similar to that of the studied patient, the breast-conserving sectionectomy surgery with subsequent follow-up was adopted, considering the reduced size of the tumor and the absence of lymph node or hematogenous dissemination[10,16].

CONCLUSION

Adenoid cystic carcinoma of the breast is part of the triple-negative tumor family and presents a paradoxically benign behavior when compared with its peers. As it is a rare tumor, the diagnosis can be facilitated through special histological techniques and the evaluation of the molecular or genomic profiling. Margin-free surgical excision is the standardized therapeutic approach, followed by clinical follow-up established between the mastologist and the patient. Although even rarer, there are records in the literature of recurrence and metastasis. Authors of the present article emphasize the importance of conducting further studies to elucidate the etiopathogenesis of breast AdCC, aiming to understand the natural history of this tumor and the mechanisms that allow it to behave differently.

AUTHORS' CONTRIBUTIONS

M.L.M.: conceptualization, data curation, investigation, methodology, project management, writing – original draft, writing – review & editing.

A.T.: resources, project administration, funding acquisition, data curation, methodology, writing – original draft, writing – review & editing.

A.A.L.L.: resources, conceptualization, methodology, supervision, writing – original draft, writing – review & editing.

C.A.S.R.: resources, formal analysis, methodology, writing – original draft, writing – review & editing.

L.C.A.: data curation, resources, writing – original draft, writing – review & editing.

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CASE REPORT
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Solid intracystic papillary carcinoma in male breast: case report

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ABSTRACT

The intracystic papillary carcinoma (IPC) is one of the rarest types of breast cancer, mainly in men, representing less than 1% of the malignant diseases in the male sex. It is frequently associated with the ductal carcinoma *in situ* (DCIS), but there are also other forms such as the pure and the invasive ones. The male population breast cancer diagnosis is late and, therefore, it has a worse prognosis. The diagnosis is given by imaging tests and anatomopathological studies. The treatment consists of excisional tumor therapy, which can be carried out conservatively or through mastectomy, with or without adjuvant therapy.

KEYWORDS: breast neoplasms, male; carcinoma, papillary; carcinoma, intraductal, noninfiltrating.

INTRODUCTION

Breast cancer in men is rare, accounting for about 1% of all breast cancers and associated with less than 0.1% mortality. Its incidence, as well as in women, is also related to age, as it mainly affects men aged over 60 years. The five-year overall and event-free survival is low, mainly due to the late diagnosis. When this diagnosis is made, a neoplasm in a more advanced stage is identified[1,2].

Intracystic papillary carcinoma (IPC) is among the rarest forms of breast cancer, with an incidence of less than 1% of breast neoplasms. It is usually verified in older women, but it also affects men, though more uncommonly. It has a good prognosis. Its 10-year survival rate is 100% and the recurrence-free rate is 95%, which shows that, despite being a rare cancer, it has a high survival rate and a low recurrence rate[1-8]. Thus, to document the occurrence of breast cancer in men is deemed very relevant to identify possible risk factors, to develop more specific therapeutic strategies and even future prevention measures.

Therefore, this study aimed to report the case of a male patient diagnosed with breast cancer, as well as his clinical history and the histological subtype of the tumor, in addition to analyzing the therapeutic approach and its follow-up.

CASE REPORT

FRS, man, 41 years old, identified the presence of a painless nodule in the left breast in the retroareolar region and sought medical care in December 2018. On that occasion, ultrasound and bilateral screening mammogram were performed, which showed, respectively, a 1.3 cm nodulation in the left breast, well-delimited, in the retroareolar, hypoechoic and Bi-rads III region, and a well-delimited nodulation in the central region of the left breast of 1.2 cm and Bi-rads 0.

Five months after undergoing these tests, the patient sought new medical care in May 2019. During this consultation, bulging in the left areolar region was identified on the physical examination, on static inspection, and its accentuation, on dynamic inspection. On palpation of the breast, a hardened nodulation of approximately 2 cm in diameter was observed in the retroareolar region, irregular and adhered to adjacent planes. In the armpits, bilateral fibroelastic lymph nodes were detected, and breast expression was negative.

After clinical evaluation, a new ultrasound was requested and a nodular growth of 0.26 cm was observed, with a new diameter of 1.56 cm. Furthermore, irregular contours and Bi-rads IVa were found, which demonstrated significant tumor growth in the last five months. An excisional biopsy was chosen for anatomopathological study due to the location and superficiality of the nodulation.

Postoperatively, the patient developed seroma and a small area of necrosis in the areolar region (Figure 1).

The anatomopathological report of the excision of the breast nodule showed an epithelial proliferative lesion with an extensive area of tumor necrosis. The residual neoplasm sample showed cells with mild atypia arranged in solid and cribriform arrangements. Mitotic figures were not observed and the surgical margins were compromised (Figure 2A).

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To confirm the diagnosis, the specimen was referred to immunohistochemical study, which showed encapsulated papillary carcinoma,[9] with an intermediate-grade ductal carcinoma *in situ* component in the adjacent parenchyma (Figure 2B). Histological sections demonstrated an extensively necrotic papillary lesion, well-delimited, consisting of fibrovascular axes covered by monotonous epithelial cells with atypia.

In the periphery of the lesion, areas of intermediate-grade solid and cribriform ductal carcinoma *in situ* were identified. No frankly-invasive carcinoma foci were identified in the sample. The presence of associated ductal carcinoma *in situ* poses greater risk of local recurrence.

The neoplasm was negative for calponin (SMMHC) and p63 protein, confirming the absence of these cells in the papillary stems and in the periphery of the lesion, negative for high molecular weight cytokeratin (CK-14), and showed strong and diffuse positivity for estrogen receptor (ER) (Figure 2B, Table 1).

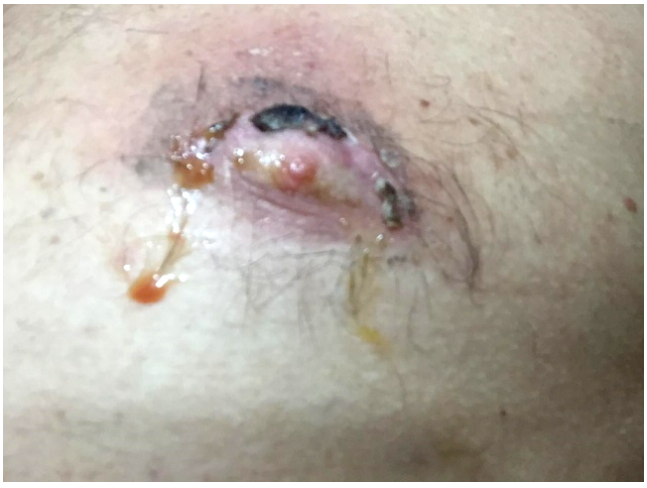


Figure 1. Patient's left breast showing postoperative changes.

The anatomopathological report also demonstrated an epithelial proliferative lesion with extensive tumor necrosis. The residual neoplasm sample showed cells with mild atypia arranged in solid and cribriform arrangements.

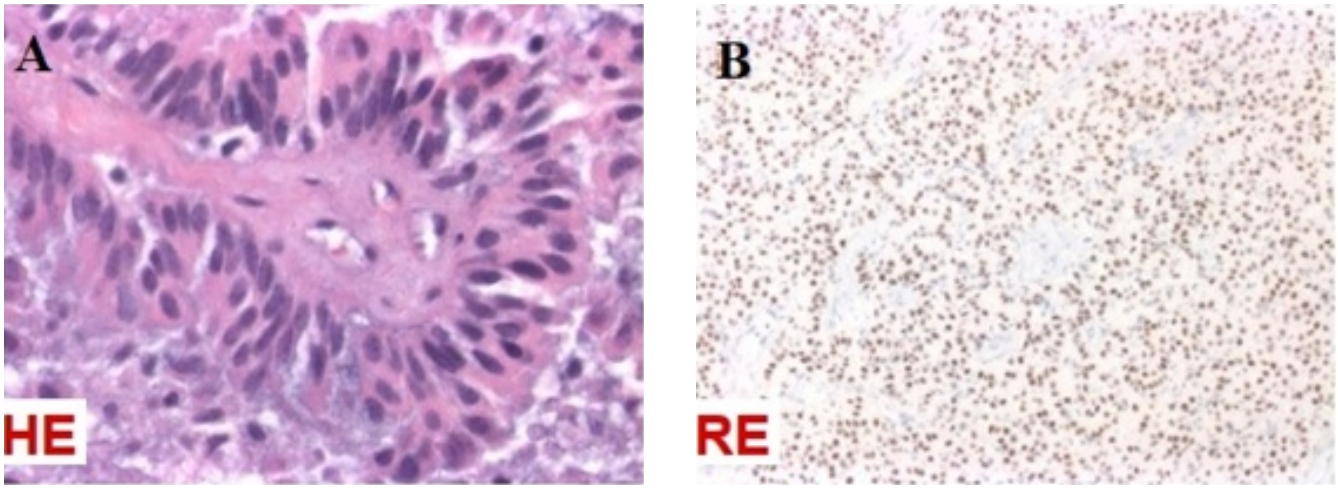
After diagnostic confirmation, the patient underwent simple mastectomy, with isotopic labeling of sentinel lymph node, and had good postoperative evolution. According to the anatomopathological study, a sentinel lymph node free of neoplastic infiltrate and the left breast without residual neoplasia were verified.

Clinical oncology evaluation was requested and Tamoxifen 20 mg/day was prescribed. The patient remained in clinical follow-up after surgery. He showed no signs of local recurrence and has been under outpatient follow-up since the time of diagnosis, in December 2018, with a total follow-up time of three years.

DISCUSSION

Intracystic papillary carcinoma (IPC) is a rare cancer, representing 1% of all types of cancer. It accounts for up to 2% of cases in women, whereas in men the incidence is less than 1%. The average age of its onset ranges from 68 to 84 years, and it mainly affects women, being unusual for men[4]. It is characterized as intracystic papillary growth carcinoma of the breast, mostly unilateral growth. The diagnosis is usually localized, without dissemination to lymph nodes or with distant metastases[3,4,10]. In the reported patient, the tumor presentation was at 41 years of age, lower than the epidemiological data, and it was well-localized and without dissemination and/or metastases.

Anatomically, this tumor usually appears macroscopically as a well-defined lesion surrounded by a fibrous capsule. Microscopically, the capsule can be filled by a fibrovascular layer, and its stroma is characterized by cells distributed in clearly papillary structures. However, they can present a malignant cellular aspect, with the presence of atypia[4,5,10].



H&E: hematoxylin and eosin staining; ER: estrogen receptors.

Figure 2. (A) Results of the histopathological study that showed, in the periphery of the lesion, areas of intermediate-grade ductal carcinoma *in situ*, solid and cribriform types; (B) Immunohistochemical study showing strong and diffuse positivity for estrogen receptors.

Histologically, IPC is divided into three subtypes: pure, IPC associated with ductal carcinoma *in situ* (DCIS), and that associated with invasive cancer[4,5,10]. IPC in its pure form is extremely rare. The most frequent form of presentation is associated with DCIS or invasive cancer. In order to differentiate the histological type, studies claim that core biopsy has proved to be effective in differentiating papillary neoplasms from other diseases and from their benign forms[6]. Addressing the nature of the carcinoma is extremely important for the prognosis, as IPC associated with DCIS becomes an important causal factor for the development of invasive carcinoma, requiring additional treatment[6].

Thus, IPC associated with DCIS refers to a more diffuse form of the disease, which involves several ducts, thus making the lesion more extensive and less localized, favoring the development of invasive carcinoma in addition to posing greater risk of local recurrence[3].

The progression of carcinoma to the invasive form can be identified by immunohistochemical study, as the high degree of cell differentiation favors the metastatic process of the tumor. The lack of a basal layer in myoepithelial cells (SMMHC) can be identified by calponin and p63, proteins present in myoepithelial cells that, when expressed, indicate that the carcinoma is not yet invasive, i.e., that it is *in situ*[3,11-13]. Hence, it is observed that the loss of the basal layer in the myoepithelial cells, i.e., the loss of expression of calponin and p63, assists in the tumor metastatic dissemination, making the carcinoma invasive. Nevertheless, the lack of expression of these receptors increases the chances of this tumor to be malignant. The identification, by immunohistochemistry, of calponin and p63 proteins is highly sensitive in detecting tumor invasion in malignant papillary breast lesions, being widely used in clinical practice[3,11-13].

Clinical, radiological and immunohistochemical findings are essential for diagnosis. Ultrasonography shows a hypoechoic area with soft tissue echoes projecting from the cyst wall and evidencing an intracystic tumor[7]. Mammography in IPC is less specific for small tumors and usually becomes inconclusive. Conversely, larger lesions can be described as dense and well-circumscribed masses. Excisional biopsy can be performed on cystic breast lesions, and the anatomopathological study associated with immunohistochemistry helps to make a definitive IPC diagnosis[3,13].

The differential diagnosis of intracystic papillary lesions is given by histopathological samples and immunohistological studies. Therefore, some authors have reported that differentiation of intracystic papillary carcinoma is also related to loss of heterozygosity (LOH) on chromosome 16q. This characteristic has become a useful marker to differentiate an intracystic papillary carcinoma from an intraductal papillary carcinoma, as it does not have LOH[7,8]. Thus, by polymerase chain reaction, it is possible to determine the malignant potential of IPC more clearly. The etiology of the lesions is paramount to verify the disease prognosis and, therefore, to analyze an additional treatment plan when feasible[6-8].

According to the literature, the detection of ER and progesterone increases the probability that the tumor will develop in a favorable way. This is because about 90% of IPC that are positive for these markers are classified as neoplasms with good prognosis[4]. Furthermore, the presence of LOH on chromosome 16q in IPC demonstrates that this tumor has a low probability of malignancy, which is an important prognostic factor. However, the negativity expressed by calponin and p63 proteins in myoepithelial cells indicates that this tumor has a greater chance of progressing to an invasive carcinoma, favoring distant metastases. Therefore, despite presenting a worse prognostic factor due to the negativity of the expression of proteins in myoepithelial cells, other factors, such as the expression of ER and the presence of LOH on chromosome 16q, cooperate for the carcinoma of the patient in question to present a good prognosis over time[11-13].

Treatment, according to some studies, should be based on the associated pathology, and there are still no definitive guidelines for treatment. Surgical excision with a safety margin for resection has become the mainstay of treatment and can be conservative or not; in the later case, a mastectomy is required[4-16].

Regarding the use of hormone replacement therapy, it is not recommended as a routine procedure, considering that there are no changes related to future prognosis. Nevertheless, concerning IPC associated with DCIS or microinvasive disease, patients may receive Tamoxifen therapy due to increased rates of tumor recurrence and the development of invasive carcinoma. Thus, additional treatment is needed to reduce tumor recurrence rates[3,16,17].

CONCLUSION

Intracystic papillary carcinoma is an extremely rare cancer, especially in men. Some immunohistochemical characteristics make this tumor associated with carcinoma *in situ* to have a better prognosis

Table 1. Result of the immunohistochemical study of the collected sample with positivity only for estrogen and androgen receptors. The remaining was negative.

Antibodies	Clone	Result	Note / Block (%)
Estrogen receptor	ER1	Positive	100; +++/+++ (A2884/19)
Cytokeratin 14	LL002	Negative	(A2884/19)
Myoepithelial cells (SMMHC)	SMMS-1	Negative, Myoep. cells	(A2884/19)
p63 protein (squamous/transitional epithelia; myoepithelial cells)	DAK-p63	Negative, Myoep. cells	(A2884/19)
Androgen receptor	F39.4.1	Positive	(A2884/19)

such as the presence of ER. Diagnostic investigation is carried out through clinical examination associated with imaging tests, which may be requested during the evaluation. In addition, anatomopathological and immunohistochemical studies can contribute to a better characterization of the carcinoma. The mainstay of initial treatment is surgical excision of the tumor, followed by systemic adjuvant therapy, using Tamoxifen, a selective ER modulator. Therefore, this drug is the most suitable for tumors that express positivity for ER and progesterone. As for radiotherapy, it has been shown to be more effective for IPC associated with DCIS, but it is more suitable for more aggressive cases associated with lymphovascular invasion.

AUTHORS' CONTRIBUTIONS

V.G.: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, investigation, project administration, supervision, validation, visualization, writing – original draft, writing — review & editing.
E.B.Q.: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, investigation, project administration, supervision, validation, visualization, writing – original draft, writing — review & editing.
F.S.L.: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, investigation, project administration, supervision, validation, visualization, writing – original draft, writing — review & editing.
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M.B.C.: Conceptualization, funding acquisition, investigation, methodology, investigation, project administration, supervision, validation, visualization, writing — review & editing.

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CASE REPORT
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Pathogenic variants in *BRCA1/2* genes among patients with triple-negative breast cancer: a case series

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ABSTRACT

Triple-negative breast cancer (TNBC) is an uncommon molecular subtype (representing 15%–20% of breast cancers) characterized by the non-expression of estrogen receptor, progesterone receptor, and human epidermal growth receptor factor 2. More aggressive and lethal, TNBC is often associated with pathogenic variants in *BRCA1/2* genes. This study aimed to describe a series of seven cases of patients with TNBC and pathogenic variants in *BRCA1/2* genes. All patients were female and under 50 years of age at diagnosis. Four of them presented a family history of breast cancer and/or other neoplasms. The predominant clinical stage was IIB, and the main anatomopathological stage was pT2pN0M0. The mean tumor size in the series was 2.5 cm (1.0 to 3.2 cm). Ki-67 was > 30% in all patients. Three cases (43%) had pathological complete response, and only one presented extensive residual disease after neoadjuvant chemotherapy. Six patients showed pathogenic variants in *BRCA1* (86%) and one in *BRCA2+* (14%). After a mean follow-up of 38 months (19 to 68 months), five patients were alive and without neoplastic disease, and two progressed to metastasis.

KEYWORDS: mutation; genes, BRCA1; genes, BRCA2; triple negative breast neoplasms; case reports.

INTRODUCTION

Triple-negative breast cancer (TNBC) is a molecular subtype characterized by the non-expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth receptor factor 2 (HER2). With a worse prognosis and lower survival, TNBC represents 15% to 20% of breast cancers and is more frequent in black and Hispanic women[1,2].

TNBC is also associated with a higher incidence of pathogenic variants in *BRCA1/2* genes, especially in *BRCA1*[3]. Study conducted by Barreta et al. showed that the overall survival (OS) of patients with no pathogenic variants in *BRCA1/2* is greater than among *BRCA1/2+* patients. However, recurrence-free survival (RFS) presented no significant difference[4].

Identifying patients with TNBC and *BRCA1/2* pathogenic variants is important because it allows defining risk-reducing surgical strategies (contralateral mastectomy and bilateral salpingo-oophorectomy) and administering systemic treatments (use of platinum agents in neoadjuvant therapies and poly [ADP-ribose] polymerase inhibitors — PARP [Olaparib] in metastatic settings)[5,6].

This study aimed to describe a series of seven cases of patients with TNBC and pathogenic variants in *BRCA1/2* genes.

CASE SERIES

As shown in Table 1, all patients were female. The mean age in the series was 37 years (28 to 48). Six patients (86%) had pathogenic variants in *BRCA1* and one (14%) in *BRCA2+*. The mean tumor size was 2.5 cm (1.0 to 3.2 cm). Five patients (71%) presented clinical stage IIB and anatomopathological stage pT2pN0M0. All of them received surgical treatment, neoadjuvant chemotherapy, and adjuvant radiotherapy. After a mean follow-up of 38 months (19 to 68 months), all patients were alive, but two presented metastatic neoplastic disease (case 5 since March 2020 and case 6 since February 2020).

Case 1 patient reported an extensive family history of breast cancer: four maternal cousins (one deceased), one paternal cousin, and a sister (diagnosed with breast cancer at 44 years of age). In addition, she had a maternal aunt with ovarian cancer (death at 74 years) and two paternal uncles with lung cancer. Case 3 patient declared as family history of cancer: her mother (diagnosed with breast cancer at 30 years of age in the 1980s, dying at the age of 36), father (lung cancer), paternal grandmother (pancreatic cancer), a maternal cousin (ovarian cancer), and a paternal aunt and paternal cousin (hematological neoplasms). Case 4 patient also

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had a family history of cancer: her father, who died as a result of prostate cancer, and a maternal aunt, who had cervical cancer. Case 5 patient did not know her family history because she is adopted and has no contact with her biological family. Case 7 patient stated that her mother was diagnosed with breast cancer at 35 years of age and died at 45.

Table 1. Description of variables associated with patients in the series.

Description / Patients	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Gender	Female	Female	Female	Female	Female	Female	Female
Age at diagnosis (years)	38	36	47	48	28	32	32
Previous pregnancies (number)	4	0	1	5	1	3	0
Comorbidities	None	None	None	None	None	None	None
Family history of breast cancer	Yes	No	Yes	No	Unknown	No	Yes
Family history of other neoplasms	Yes	No	Yes	Yes	Unknown	No	No
Histological type	NST	NST	NST	NST	NST	NST	NST
Tumor size (cm)	2.5	2.3	1.0	2.8	3.2	2.8	2.9
Cell differentiation grade	G3	G2	G2	G3	G3	G2	G2
Angiolymphatic invasion	No	No	No	No	No	Yes	No
Perineural invasion	No	No	No	No	No	No	No
Ki-67 (%)	60	40	40	70	90	80	40
Molecular subtype	TN	TN	TN	TN	TN	TN	TN
Axillary involvement (number of lymph nodes)	No	No	No	No	Yes (4)	No	No
Metastasis at diagnosis	No	No	No	No	No	No	No
Clinical stage	IIB	IIB	IB	IIB	IIIC	IIB	IIB
Anatomopathological stage	pT2pN0M0	pT2pN0M0	pT1pN0M0	pT2pN0M0	pT2pN2M0	pT2pN0M0	pT2pN0M0
Surgical treatment	M+SLN+AD	M+SLN	M+SLN	SR+SLN	M+SLN+AD	SR+SLN	M+SLN
Contralateral mastectomy	Yes	Yes	Yes	No	Yes	No	Yes
Salpingo-oophorectomy	No	No	Yes	Yes	No	Yes	No
Complementary treatment	NACT+ART	NACT+ART	NACT+ART	NACT+ART	NACT+ART	NACT+ART	NACT+ART
Immunotherapy	No	No	No	No	No	No	No
Olaparib	No	No	No	No	Yes	Yes	No
Sentinel lymph node	Negative	Negative	Negative	Negative	Positive	Negative	Negative
Pathological response	pCR	pCR	RCB-II	RCB-I	RCB-III	RCB-II	pCR
Pathogenic mutations (*BRCA1/2*)	***BRCA1***	***BRCA1***	***BRCA1***	***BRCA2***	***BRCA1***	***BRCA1***	***BRCA1***
Clinical course	ADF	ADF	ADF	ADF	Metastasis	Metastasis	ADF

NST: invasive carcinoma of no special type; TN: triple-negative; M: mastectomy; SR: segmental resection; SLN: sentinel lymph node; AD: axillary drainage; NACT: neoadjuvant chemotherapy; ART: adjuvant radiotherapy; pCR: pathological complete response; RCB-I: minimal residual cancer burden; RCB-II: moderate residual cancer burden; RCB-III: extensive residual cancer burden; ADF: alive and disease-free.

Table 2. Description of *BRCA1/2* pathogenic variants detected in the patients in the series.

Patient	Gene	Pathogenic variant (allele profile)	Protein	Molecular consequence	Accession number in ClinVar
Case 1	***BRCA1***	c.3331_3334del (heterozygosity)	p.Gln1111fs	Frameshift	VCV000037523.14
Case 2	***BRCA1***	c.5266dupC (heterozygosity)	p.Gln1756fs	*	VCV000017677.29
Case 3	***BRCA1***	c.3331_3334del (heterozygosity)	p.Gln1111fs	Frameshift	VCV000037523.14
Case 4	***BRCA2***	c.2167delA (heterozygosity)	*	*	New (not described in ClinVar)
Case 5	***BRCA1***	c.4675+1G>A (heterozygosity)	*	Splice donor	VCV000055256.15
Case 6	***BRCA1***	c.655G>A (heterozygosity)	p.Asp219Asn	Missense	VCV000055655.7
Case 7	***BRCA1***	c.3331_3334del (heterozygosity)	p.Gln1111fs	Frameshift	VCV000037523.14

*No associated data in ClinVar (https://ncbi.nlm.nih.gov/clinvar/).

Table 2 shows the *BRCA1/2* pathogenic variants found. Among the *BRCA1* pathogenic variants, three corresponded to the identical frameshift type (c.3331_3334del [p.Gln1111fs] in heterozygosity, determining a truncated protein), and these probands were not from related families.

This case series originated from a study based on medical records of patients diagnosed with breast cancer, part of a scientific project approved by the Research Ethics Committee (REC) of the Universidade Estadual do Piauí, Teresina (Piauí), Brazil, under the Certificate of Presentation for Ethical Consideration (*Certificado de Apresentação para Apreciação Ética* — CAAE) No. 30154720.0.0000.5209. All Brazilian ethical directives on research were observed (National Health Council Resolution No. 466/12).

DISCUSSION

In this study, all patients were under 50 years of age at diagnosis. Robertson et al. performed the genetic analysis of 308 patients with TNBC and found 45 cases with *BRCA1* pathogenic variants. They concluded that the chances of patients with TN tumors having *BRCA1* pathogenic variants are higher before the age of 50 years (above 10%). This finding justifies the National Comprehensive Cancer Network (NCCN) recommendation to test all patients diagnosed with TNBC before the age of 60 for *BRCA1/2*[7-9].

Among the six patients who knew their family history, four presented a family history of breast cancer and/or other neoplasms. Family history is a known risk factor for the development of breast cancer, with higher frequency in patients with *BRCA1/2* pathogenic variants, which also occurred in this study[10].

After univariate and multivariate analyses, Lopes et al. showed that angiolymphatic invasion and larger tumor size were factors associated with worse prognosis in TNBC[11]. In this series, the two cases that progressed to metastasis presented tumor sizes larger than the mean of the series (2.5 cm), and case 6, who progressed to metastasis, showed angiolymphatic invasion.

Ki-67 is an important prognostic factor related to worse TNBC progression[12]. However, greater knowledge about its cut-off point is needed, with some studies indicating a value of approximately 30%[13,14]. In this series, all patients had Ki-67 values >30%.

Silva et al. revealed that TNBC is a predictive factor for pathological complete response (pCR), occurring in about 40% of these patients[15]. Other studies also associate TN tumors in patients with *BRCA1/2* pathogenic variants with higher chemoresponsiveness[16,17]. In this study, three patients (43%) had pCR, and only one presented extensive residual disease (residual cancer burden — RCB-III) after neoadjuvant chemotherapy, ratifying literature data.

Six patients showed pathogenic variants in *BRCA1* and one in *BRCA2*. The literature also indicates a higher prevalence of *BRCA1* in young women diagnosed with TNBC compared to *BRCA2*[18,19]. Case 4 presented the novel pathogenic variant c.2167delA in *BRCA2* (not yet described in ClinVar). Nonetheless, this variant has been described in the literature. In the study by Palmero et al. on *BRCA1/2* pathogenic variants in 649 probands of 28 centers from 11 Brazilian states, the authors analyzed 208 *BRCA2*+ probands and also found the pathogenic variant c.2167delA in one of them[20].

Literature data indicate that patients with *BRCA1* and *BRCA2* pathogenic variants have a 27% and 19% probability of developing contralateral breast cancer after primary tumor surgery in the ipsilateral breast, while this risk is only 5% in the general population. At the same time, contralateral mastectomy shows no benefits regarding OS in these patients. In turn, bilateral salpingo-oophorectomy reduces the risk of cancer recurrence in the ipsilateral and contralateral breast in *BRCA1/2*+ patients, improving their OS. Bilateral salpingo-oophorectomy also decreases the likelihood of ovarian cancer by more than 80% in *BRCA1/2*+ patients[21]. In addition, risk-reducing surgical strategies are more beneficial to younger patients with TNBC and *BRCA1/2*+ and with pCR after neoadjuvant chemotherapy[5]. In this study, all patients underwent risk-reducing contralateral mastectomy and/or bilateral salpingo-oophorectomy.

After a mean follow-up of 38 months (19 to 68 months), five patients were alive and disease-free, while two progressed to metastasis before five years from diagnosis. The literature associates TNBC with worse clinical course and lower survival. However, immunotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors have also improved the prognosis of patients with TN tumors and *BRCA1/2* pathogenic variants[22,23]. In this series, case 5 developed metastasis to lymph nodes, lungs, adrenal glands, and bones 20 months after the initial diagnosis, and case 6 developed metastasis to lymph nodes and the central nervous system 41 months after the initial diagnosis. Olaparib (a PARP inhibitor) was administered as a therapeutic option for these two patients after metastasis. Both patients (cases 5 and 6) are still alive and on clinical follow-up 9 and 10 months after systemic recurrence, respectively.

The limitations of this study include the sample size and being performed in a single oncology center.

CONCLUSION

Among the seven patients with TNBC and *BRCA1/2* pathogenic variants in this series (all women, with a mean age of 37 years and mean tumor size of 2.5 cm), three (43%) presented pCR, and only one had RCB-III after neoadjuvant chemotherapy. The mean follow-up time was 38 months. At the end of follow-up, all patients were alive, and two presented systemic neoplastic disease before five years from diagnosis.

AUTHORS' CONTRIBUTIONS

R.E.A.R.C.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing — original draft, Writing — review & editing.

F.T.R.O.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft.

A.L.N.A.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

S.C.V.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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CASE REPORT
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Necrotizing fasciitis of the breast: case report

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ABSTRACT

Necrotizing fasciitis is a severe soft tissue infection characterized by rapidly progressive diffuse necrosis of fascia and adjacent tissues, most reported in the abdominal wall, perineum, and extremities. Cases of idiopathic necrotizing fasciitis of the breast are rare and unrelated to risk factors. This study was conducted with a 19-year-old woman reporting mastalgia and phlogistic signs in her right breast, which evolved with serosanguineous blisters and extensive necrosis of the fascia and periareolar wall, characterizing the necrotizing fasciitis. Therefore, the authors aim to show the relevance of early diagnosis associated with prompt treatment and procedure for a better intervention outcome.

KEYWORDS: fasciitis, necrotizing; breast; infections.

INTRODUCTION

Necrotizing fasciitis (NF) is a severe soft tissue infection characterized by rapidly progressive diffuse necrosis of fascia and adjacent tissues[1]. Primary NF of the breast without an inciting event is an extremely rare association, with a total of 25 cases found in the literature[2]. Early diagnosis and prompt treatment are essential to reduce the morbidity of NF[1,3].

A review of the interdisciplinary electronic databases National Library of Medicine (PubMed), Scientific Electronic Library Online (SciELO), Virtual Health Library (VHL), and Latin American and Caribbean Health Sciences Literature (LILACS) was carried out using the following search terms: "Necrotizing fasciitis," "breast," and "infections," both in Portuguese and English languages.

This descriptive and observational case report, in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki)[4] and the Resolution of the Brazilian Federal Council of Medicine in 1595/2000[5], was approved by the Ethics Committee for Research involving Human Beings from Centro Universitário de Volta Redonda upon Certificate of Presentation for Ethical Appreciation (CAAE) 47301421.5.0000.5237, on June 2, 2021.

CASE REPORT

G.C.R.C., woman, aged 19 years, mixed-race, single, born and resident in the state of Rio de Janeiro (RJ), Brazil. She was admitted to the emergency room (ER) of Hospital São João Batista (HSJB), in the city of Volta Redonda (RJ), on February 22, 2021, reporting mastalgia and phlogistic signs in her right breast for three days, with no preexisting trauma or local wound, associated with fever (without checking the temperature with a thermometer).

The patient is a smoker and denied any history of comorbidities, malignant neoplasms, surgical procedures, or previous gestational history.

On physical examination, she was in regular general condition, with hyperemia of the right breast in the periareolar region, with lateral spread of the inflammatory process. Nipple piercing, implanted two years earlier, was noted, which was removed during the approach.

Upon admission, laboratory tests were requested, whose results showed: 4,000,000/mm^3 red blood cells; 10.4g% hemoglobin; 21,200/mm^3 leukocytes (1,696 bands, 15,476 polys, 2,756 lymphocytes, 1,272 monocytes); 108,000/mm^3 platelets; 102 mg/dL blood glucose; 43 mg/dL urea; 0.8 mg/dL creatinine; 46.9 mg/dL C-reactive protein (CRP). After laboratory analysis, under the diagnostic hypothesis of cellulitis, the patient was discharged with prescription of oral amoxicillin and analgesics.

On February 24, two days after being seen at the ER, the patient returned to the unit and was admitted to the Department of Gynecology and Obstetrics (GO). The course of treatment was based on the request for breast ultrasound, the suspension of amoxicillin, the prescription of oxacillin and symptomatic treatment.

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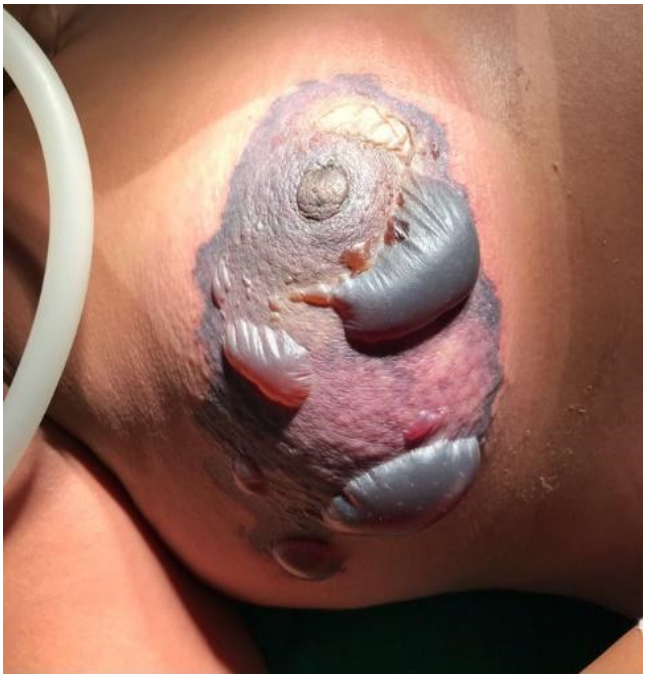
Four hours after admission, the patient developed with periareolar ecchymosis, serosanguineous blisters, and periareolar necrosis (Figure 1). Thus, considering the rapid evolution, the diagnostic hypothesis of NF with extensive cellulitis was established.

On the day after admission, a breast ultrasound was performed, which showed heterogeneous glandular breast parenchyma with edema in the lower and upper lateral quadrants. The presence of axillary lymphadenopathy in the right side was also verified.

Metronidazole was promptly introduced to the therapeutic regimen, maintaining oxacillin, symptomatic treatment, and hospital surveillance. Upon evaluation, there was worsening of the ecchymosis and phlogistic signs. Tests requested during the day showed thrombocytopenia with the need for platelet transfusion, which was subsequently performed. In addition, a decrease in the number of leukocytes and an increase in CRP were identified.

An opinion was requested from the Department of Internal Medicine, which, together with the GO department, started monitoring the young woman. Such departments, isochronally, opted for suspending the use of oxacillin and metronidazole and began to administer teicoplanin and cefepime.

On the third day, the patient underwent surgical debridement with fasciotomy and removal of necrotic tissue (Figure 2). Prior to surgery, cefazolin was administered to the patient, in addition to performing skin asepsis and antisepsis. The operation was uneventful and allowed collecting serum from inside the blisters, which was directed to culture, histopathology, and cytology tests.



Source: HSJB medical team.

Figure 1. Department of Gynecology and Obstetrics on February 24, 2021, at the time of immediate preoperative, blisters can be noted.

Following debridement, upon presenting with hypotension, altered level of consciousness, and signs of skin sepsis, the patient was referred to the Intensive Care Unit (ICU). In the ICU, antibiotic therapy with clindamycin was introduced and the daily change of the wound dressing based on silver sulfadiazine was recommended. The patient required contact precautions after verifying colonization by extended-spectrum beta-lactamase (ESBL), *Klebsiella pneumoniae* Carbapenemase (KPC), and Vancomycin-resistant enterococci (VRE) by rectal swab. She remained in the ICU for seven days and, after the septic condition had improved, she was discharged to the GO ward.

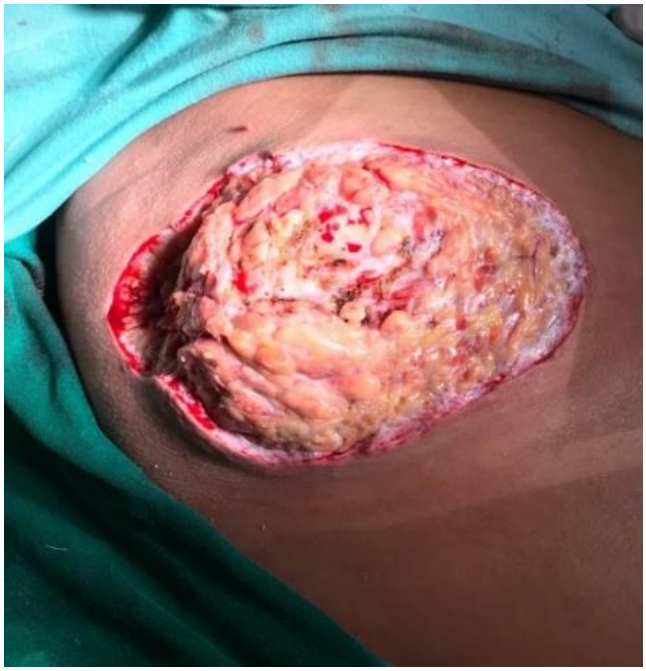
No bacterial growth was found in the culture, and the anatomopathological examination of the fascia confirmed an acute suppurative inflammatory process, with necrosis and hemorrhage.

In the ward, the patient received antibiotic therapy for 14 days. The clinical condition evidenced progressive involution with reduced seropurulent secretions and inflammatory signs. At the end of the antimicrobial therapy, the patient was discharged from the hospital and kept under outpatient follow-up.

On April 12, she underwent reconstructive plastic surgery. A skin graft was performed with the infraumbilical region as the donor site. The procedure was uneventful (Figure 3).

DISCUSSION

NF is a rare (0.4 cases in 100,000 individuals), aggressive infection with high mortality rates[6]. Predisposing conditions include: chronic or immunosuppressive diseases, alcohol abuse, surgeries, penetrating and closed skin wounds and trauma, or even a minimal skin injury[7,8].



Source: HSJB medical team.

Figure 2. Operating Room on February 27, 2021, at the time of postoperative debridement.

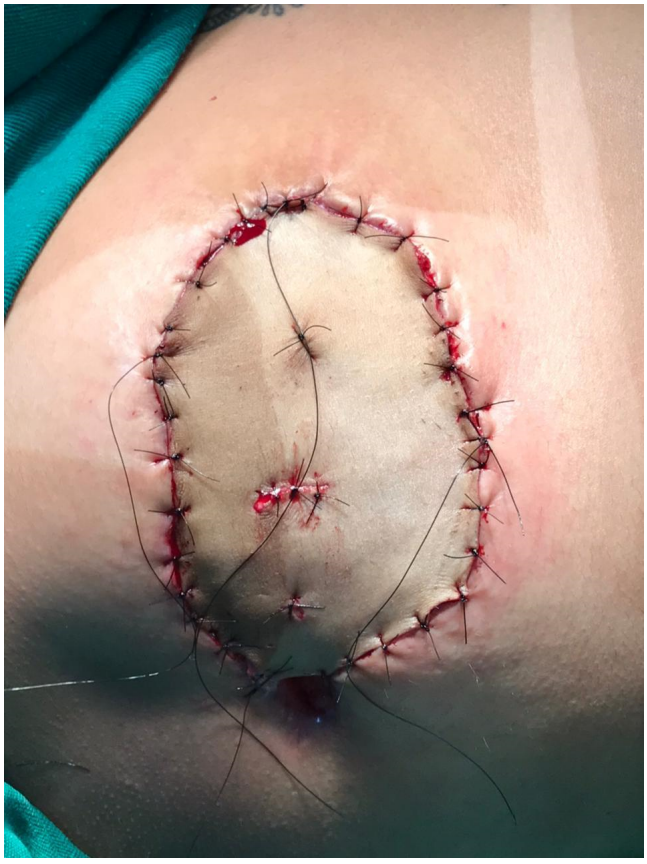
Streptococcus pyogenes and *Staphylococcus aureus*, alone or in association, usually are the etiological agents[2,9].

Acute necrotizing inflammation affects the subcutaneous tissue and fascia. More superficial tissues and skin are secondarily affected, subsequent to vascular trauma, thrombosis, and ischemia[3].

NF clinically manifests as an erythematous, painful, and localized area correlated with edema, evolving with local cyanosis and blister formation. The impaired area becomes delimited, surrounded by erythematous borders and lined with necrotic tissue. Then, it progresses with the destruction of the underlying subcutaneous tissues and with thrombosis, resulting in necrosis. The lack of treatment can increase the secondary involvement of the muscle layer, even causing myositis or myonecrosis[8].

Diagnosis is based on clinical findings, corroborated by surgical ones, which include insufficient adherence of the subcutaneous tissue, no bleeding, and subcutaneous liquefactive necrosis. Moreover, serum laboratory abnormalities may support the diagnostic hypothesis, such as: anemia; leukocytosis with left shift; elevated CRP, erythrocyte sedimentation rate (ESR), and creatine phosphokinase (CPK); and hyperglycemia[3].

Blood cultures and cultures can aid in the identification of microorganisms and sensitivity to antibiotics. Imaging methods can provide additional considerations. Fascia biopsy is considered the gold standard and should be performed in all patients during debridement[3].



Source: HSJB medical team.

Figure 3. Operating Room on April 12, 2021; the result of breast reconstruction with a skin graft can be observed.

NF is a surgical emergency, in such a way early diagnosis and prompt treatment are essential to reduce morbidity[1]. Once the diagnosis is made, treatment must immediately starts and include: volume replacement, surgical debridement, use of broad-spectrum antibiotic therapy, and psychological support[3]. After surgical treatment and definition of tissue integrity, skin reconstruction and skin grafts should be scheduled[10].

The patient of the present report developed NF unrelated to risk factors. Thus, although it can occur in any anatomical site, breast involvement is extremely rare. It was first described in the literature by Shah et al.[11] and there are about 20 reports of primary breast infection occurring in previously healthy non-lactating women.

Considering the rarity of the pathology and the diagnostic difficulty, the diagnosis is usually late and results in an unusual management plan, with uncontrolled and severe progression of the disease[12].

The authors ratify the importance of early diagnosis and prompt therapy for an adequate outcome. It is essential to exclude differential diagnoses, considering that the severity and speed of progression, with evolution time inversely proportional to survival rates, justifies the use of broad-spectrum antibiotic therapy, surgical debridement, and support in ICU to avoid complications and eventual lethality[6].

CONCLUSION

This report, according to the literature, presents one of the youngest patients to develop primary idiopathic necrotizing fasciitis of the breast. Thus, it describes a rare, serious, and uncommon case of infection in a previously healthy young woman. Therefore, even in healthy patients and in the absence of associated risk factors, NF can present itself as a rapidly progressive and destructive condition. Considering the aggressive nature of the disease, resulting from the difficult and challenging clinical suspicion, early diagnosis and rapid and appropriate intervention are essential to reduce its morbidity and mortality.

AUTHORS' CONTRIBUTIONS

A.P.C.: Conceptualization, Investigation, Project administration, Supervision, Validation.
R.P.S.: Investigation, Project administration, Supervision, Validation.
J.V.M.V.: Methodology, Research, Writing — original draft, Writing — review & editing.
A.M.V.: Research, Writing — review & editing.
F.R.X.: Writing — review & editing.
L.V.R.: Writing — review & editing.
M.C.S.B.: Writing — review & editing.
V.E.V.: Writing — review & editing.

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CASE REPORT
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Primary breast MALT lymphoma: a case report

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ABSTRACT

A 42-year-old woman, with no history of autoimmune diseases or risk factors for cancer, sought a private medical clinic for undergoing breast imaging tests, noticing the presence of a solid nodule with indistinct margins — BI-RADS 4 — in the left breast. An ultrasound-guided core biopsy was performed and complemented by histopathological and immunohistochemical studies, confirming the diagnosis of primary small B-cell MALT lymphoma. After treatment with radiotherapy, the patient evolved with remission, maintaining annual follow-up with a specialist physician. The importance of routine screening for pathologies that affect the breasts is highlighted, aiming at their early diagnosis. In addition, radiotherapy has good prognostic results at the expense of surgical treatment.

KEYWORDS: lymphoma, B-cell. marginal zone; breast neoplasms; radiotherapy.

INTRODUCTION

Primary breast lymphoma (PBL) is a rare manifestation of breast cancer, accounting for 0.4%–0.5% of all malignant breast lesions[1]. Despite presenting clinical characteristics of other types of breast cancer, PBL occurs without evidence of systemic disease[2]. In addition, it is characterized by the presence of breast tissue associated with lymphocytic infiltrate and by the presence of ipsilateral axillary lymphadenopathy of the primary lesion[3].

The most common type of PBL is the non-Hodgkin diffuse large B-cell lymphoma, accounting for 50% of all PBL cases and 2% of all extranodal lymphomas. About 15% of PBL are of the follicular subtype; 12%, of the mucosa-associated lymphoid tissue lymphoma (MALT) type; and 16%, of Burkitt and Burkitt-like lymphoma type[4].

The mean age at PBL diagnosis is 68 years, being prevalent in women, which suggests a relation with the female hormone estrogen. Patients may present with symptoms such as local pain or inflammation, palpable lymph nodes, or painless masses in the outer quadrant of the affected breast; however, asymptomatic cases are more prevalent. In these asymptomatic cases, the diagnostic suspicion is evidenced after undertaking a mammogram test showing incidental findings such as noncalcified soft solitary masses[5].

After performing fine-needle aspiration, or core biopsy, for histopathological analysis, the diagnosis can be confirmed, requiring an active search for primary sites of cancer, especially in the gastrointestinal tract (GIT). Computed tomography (CT) or magnetic resonance imaging (MRI) are performed to rule out metastases and confirm the primary site[6].

Surgical treatment has been losing ground in the scientific community, considering that it does not show benefits when compared with radiotherapy or chemotherapy. Therefore, for localized cases of MALT lymphoma, treatment based on radiotherapy is indicated, whereas for more advanced cases, radiotherapy is adopted in combination with chemotherapy. Additional predictive factors for the disease staging include age, numbers of extranodal sites, course of treatment, and levels of lactate dehydrogenase (LDH)[7].

The present study aimed to report the case of an unusual presentation of oncological disease, a primary breast MALT lymphoma, seeking to evidence the importance of adequate follow-up for the patient's good prognosis.

CASE REPORT

This is a case report of a woman, aged 42 years, white, with no medical history of interest, with a G2P2A0 obstetric history, who

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gave birth for the last time 14 years ago, in addition to denying smoking or other risk factors for oncological diseases. The patient sought a private medical service for routine mammography. Heterogeneously dense breast tissue and the presence of normal lymph nodes in the left axillary extension were observed; no nodular images were detected due to the high density of the breast tissue, and the examination was complemented by breast ultrasound for comparative study.

According to the ultrasound results, there was a solid, hypoechoic nodule with regular contours, located in the right breast at 1-o'clock position, measuring 0.8 × 0.4 × 0.8 cm, 1.2 cm from its center to the skin. A solid, hypoechoic nodule with indistinct margins was also observed, located in the left breast at 1/2 o'clock position, measuring 2.0 × 0.8 × 1.8 cm, 1.2 cm from its center to the skin. After comparing mammography and ultrasound tests, the patient was classified as BI-RADS 4 and proceeded to diagnostic investigation, undergoing an ultrasound-guided core biopsy two days later. Four fragments were removed with a 14-gauge needle, from both lesions, for anatomopathological study; the right breast nodule being classified as intra- and pericanalicular fibroadenoma (Figure 1).

On the left breast, lymphocyte proliferation was observed, including sparse reactive follicles, with a predominance of mature lymphocytes, mainly affecting the periductal stroma, intraepithelial lymphocytes (Figure 2).

With the differential diagnosis proposed by the pathologist between chronic mastitis and low-grade lymphoma, an immunohistochemical study was carried out.

According to immunohistochemical examination, the presence of a dense lymphocytic infiltrate in the breast parenchyma was verified, consisting of small atypical B cells (CD20+), several lymphoid follicles with prominent germinal centers, and numerous foci of lymphoepithelial lesions that are highlighted by immunostaining for cytokeratin and CD20. A low cell proliferation index was also observed in the monocytoid lymphoid population. The set of findings elucidated the diagnosis of primary small B-cell MALT lymphoma of the breast. B cells were positive for CD20 and CD10, but negative for CD3 (Table 1).

Upon diagnosis, the patient underwent positron emission tomography (PET-CT) to investigate additional lesions, in which no additional mass or lymphadenopathies were observed (Figure 3).

After staging of the lesion and deciding on the appropriate therapy, the patient started radiotherapy treatment with a total dose of 4140 cGy during 23 sessions, with no complications. Nowadays, about five years after the initial investigation, the patient is in remission carrying out annual follow-up with a specialist physician, with no new neoplasms or metastases having appeared.

DISCUSSION

MALT lymphomas are indolent extranodal neoplasms that can be manifested in a wide variety of organs, including stomach, large or small intestine, lungs, salivary glands, thyroid, skin, thymus, tonsils, liver, kidney, bladder, and breast. They represent a subset of low-grade B-cell lymphomas and account for 7%–8% of all types of B-cell lymphomas and 12% of all PBL. The breast involvement of adjacent lymph nodes can be explained by the origin of the MALT from the mammary ducts and lobules, in addition to the intramammary lymph nodes[4,8].

Once in the breast, these lymphomas mainly affect women with an average age of 68 years (47–92), being especially observed during pregnancy or postpartum, and may be related to personal antecedents such as autoimmune diseases. However, this does not apply to the case in question, as the patient was diagnosed with the disease at 42 years of age and had no history of autoimmune diseases or recent pregnancy. Usually, the neoplasm presents itself as a large unilateral and painless mass, rarely bilateral, and with an average size of 3 cm[9,10].

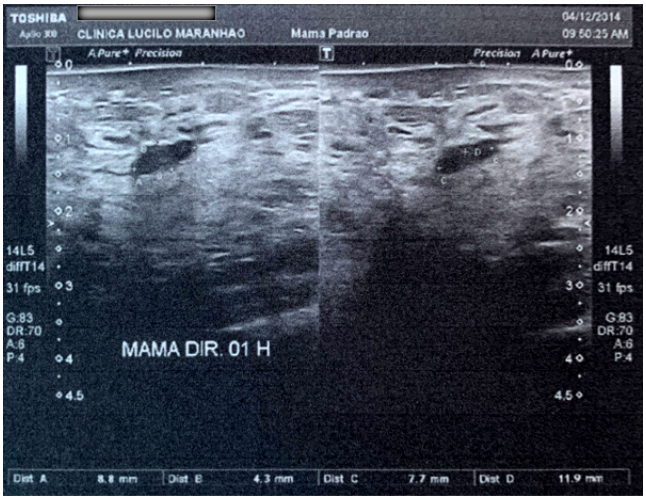

Figure 1. Right breast nodule.

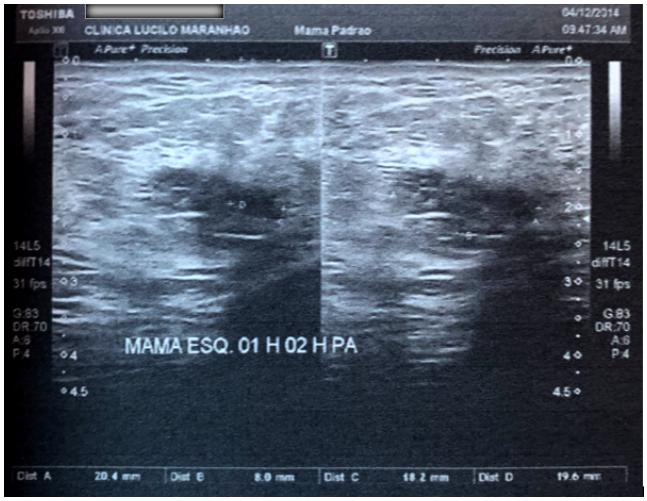

Figure 2. Left breast nodule.

Considering the clinical characteristics, the patient remains in accordance with the literature, being asymptomatic, including without presenting the classic B symptoms — systemic symptoms of fever, night sweat, and unexplained loss of more than 10% of weight in six months —, being the tumor identified as an incidental finding in imaging tests[1,9,10].

The diagnosis of PBL follows the criteria defined by Wiseman and Liao, according to which the patient must present with an appropriate specimen for diagnosis, have lymphocytic infiltrate and breast tissue in close proximity, show no evidence of concomitant systemic disease, and have no prior diagnosis of extramammary lymphoma[8].

Imaging tests are very useful to aid in making the diagnosis, considering that most patients are asymptomatic. On mammography, it appears as a solitary, noncalcified mass in about 60%–70% of cases, whereas on ultrasound it does not present specific findings[8].

After confirming the diagnosis of the tumor, having performed a histopathological analysis and an immunohistochemical study, other primary sites of the disease must be investigated to exclude the hypothesis of metastasis, with imaging tests such as MRI or CT. In the present case, the patient underwent PET-CT, a test that differs from conventional CT due to its properties of observing the metabolism of the site analyzed in the image, which did not locate additional lymphadenopathies[11].

Disease staging is based on the Ann Harbor criteria, considering the involvement of lymph chains above the diaphragm and solid organs to define severity. Stages 1 and 2 define local diseases, as in the case in question, whereas stages 3 and 4 concern cases of systemically advanced diseases[12].

Currently, there is no consensus in the literature regarding the best generalized therapeutic approach, as each case will depend on the biological behavior and histological characteristics of each lymphoma of the patients[9,10].

For more indolent and localized lymphomas, radiotherapy alone or surgery are the best forms of intervention, with surgical treatment increasingly losing ground in the scientific field, as it does not have a higher survival rate or advantages in general when compared with radiotherapy. In these less aggressive cases, radiotherapy with a mean dose between 25–30 Gy has been adopted. Chemotherapy-based treatments have been preferred for cases of more aggressive and systemic tumors, and are deemed as the best choice both alone and in combination with other therapeutic approaches[7-10].

The prognosis of patients affected by breast lymphomas will depend on their age, predictive factors, number of extranodal sites, course of treatment, and levels of LDH. It is estimated that the 5-year survival rate for patients with PBL is around 70%[7].

CONCLUSION

PBL represents a rare type of breast tumor, with clinical features of other breast neoplasms. Although uncommon, its incidence has been growing in recent years, evidencing the importance of its inclusion in the differential diagnosis of breast cancer,

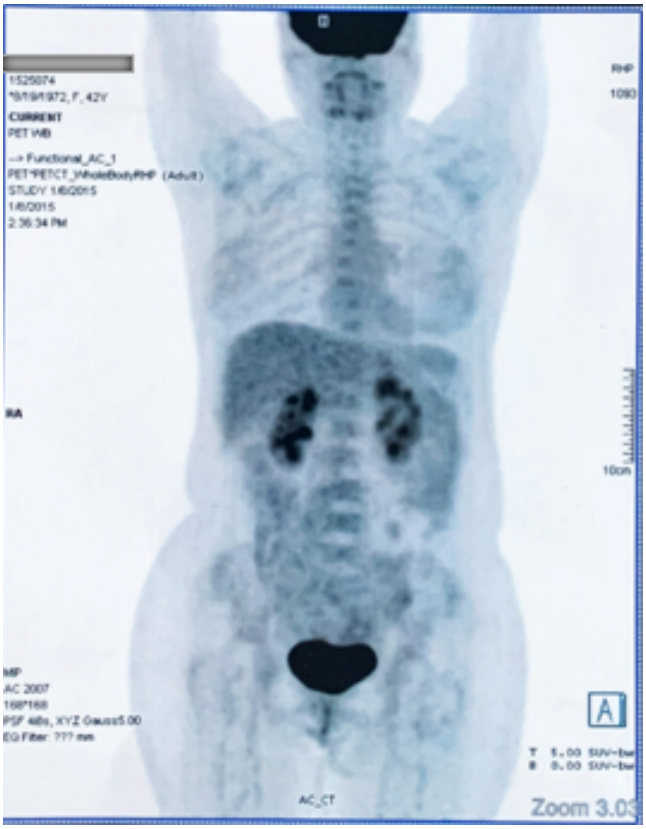

Figure 3. PET-CT coronal section, no additional mass or lymphadenopathy.

Table 1. Result of the immunohistochemical study.

Antibodies	Clone	Result	Observation
CD20 – B lymphocyte antigen	L26	Positive	
CD3 – T-cell receptor (epislon chain)	Polyclonal	Negative	
40, 48, 50, and 50.6 kDa cytokeratins	AE1/AE3	Positive	Epithelial cells
Ki-67 (cell proliferation antigen)	M1B1	Positive	5%, lymphoid cells
CD10 – Common acute lymphoblastic leukemia antigen (CALLA)	56C6	Positive	Follicular center cells
Cyclin-D1 – cell cycle regulatory protein (bcl-1)	SP4	Negative	

especially in the case of older patients. Considering that most cases are asymptomatic, the importance of breast exams and routine screening is emphasized.

AUTHORS' CONTRIBUTION

P.T.F.: Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Writing — Original Draft, Writing — Review & Editing.
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SHORT COMMUNICATION
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Breast cancer staging in population-based registries: an alert to the quality of information

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ABSTRACT

Objective: To discuss the practical difficulties associated with breast cancer staging, especially in the context of population-based cancer registries (PBCR). **Methods:** This is a short communication that discusses the importance and temporal evolution of breast cancer staging, as well as the limitations and new challenges associated with this process. **Results:** This study discusses the importance and temporal evolution of breast cancer staging, as well as the limitations and new challenges associated with this process. Minimal divergences in physical examination and disagreements in imaging tests can classify the patient in a higher or lower stage of the disease. In some population-based registries, up to 20% of the information regarding the clinical stage of breast cancer may be mistaken. **Conclusion:** We highlight the necessity for continuing education and constant training for all professionals involved in the breast cancer epidemiological context. The utilization of new technologies can help standardize the information and reduce the divergences related to cancer staging registry.

KEYWORDS: breast neoplasms; neoplasm staging; registries; evidence-based practice.

INTRODUCTION

Clinical staging plays an important role in the therapeutic planning and prognostic evaluation of patients with breast cancer[1]. This staging usually follows the TNM (primary tumor [T], regional lymph nodes [N], distant metastases [M]) system of the American Joint Committee on Cancer (AJCC), whose classification criteria are periodically updated based on scientific evidence[2,3]. However, only 23% of population-based cancer registries (PBCR) that participate in the Cancer Incidence in Five Continents, Volume IX (CI5-IX) have declared to collect TNM staging for all tumor sites[4-7].

The staging process is especially important in the critical assessment of survival curves and other epidemiological variables obtained from PBCR[2,7]. Lack of standardization hinders the epidemiological analysis of different populations and can interfere in the interpretation and development of public policies related to malignant neoplasms[6,8]. As an example, we can underline a recent divergence observed in breast cancer survival rates in the city of Goiânia, Brazil. In the CONCORD-2 study, the net survival rate for patients diagnosed with breast cancer was 79.4% between 1995 and 1999, 63.9% between 2000 and 2004, and 59.2% between 2005 and 2009[9]. However, using data from the local cancer registry, the time trends in 5-year overall survival rates were very different: 57.0% survival rate between 1988 and 1990[10], 65.4% between 1990 and 1994[11], and 72.1% between 1995 and 2003[12]. According to the authors of the CONCORD-2 study, the estimates for breast cancer survival in Goiânia were less reliable than would be preferred[13]. This divergence should not be a true epidemiological event but a methodological limitation[14].

In this context, PBCR must follow international good practice recommendations to ensure satisfactory performance quality, operationalization, and data quality[8,15,16]. These parameters range from the percentage of cases collected through histopathological tests[16] to the organization of flow diagrams for each neoplasm[17,18].

Each registry is responsible for the criteria employed to verify the quality of the clinical data collected, which are usually not reported adequately. In most registries, the person responsible for gathering information is a non-medical professional, advised by a multidisciplinary team of specialists. Despite the constant personnel training, some mistakes still occur due to the increasing

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complexity of the tumor staging process. Medical staff can also make mistakes in the staging, particularly when they gather and enter the data. This scenario may justify the high rates of "incomplete data" regarding tumor staging in different international series, usually ranging from 5% to 20%[19-21].

PRACTICAL DIFFICULTIES IN BREAST CANCER STAGING

Cancer staging estimates the extension of the neoplasm within the person's body. Despite the particularities of each tumor site, a report is usually issued after a physical examination. This report could include specific complementary tests, such as biochemical tests, computed tomography, among others[22]. However, in a real-world scenario, several factors can limit or hinder this staging process[6,8].

Concerning breast cancer staging, inter-observer variation must be highlighted in tumor measurement and clinical assessment of patients. In this context, if tumor palpation changes from 5.0 cm to 5.1 cm, cancer staging also changes, along with the prognostic classification. The assessment of lymph node status often shows divergences regarding small palpable axillary lymph nodes, which could represent a reactional inflammatory state (cN0) or one isolated axillary lymph node affected (cN1). Table 1 describes some situations that result from divergences in the staging process, with some considerations and good practice recommendations.

In most developing countries, the population can experience difficulties in accessing health services, which could extend the waiting time for complementary tests[23]. In these situations, the clinical staging of the patient is only concluded after two or three medical consultations and, occasionally, after cancer treatment begins. This fact hinders the staging process, as the patient can present significant variations in physical examinations during the investigation period, generally related to the progression of the disease. Effectively, choosing the best moment to register a variable can become a subjective decision: date of the first consultation? After the completion of complementary tests? Before starting treatment? Or should we always consider the most advanced staging?

Finally, another common situation in regions with hierarchical health systems is referring patients who received treatment from other services to reference centers after a breast cancer diagnosis. In this context, the dialog between the respective assistant professionals regarding the initial physical examination of the patient can prevent the use of the terms cTx and cNx, which would render the patient's initial staging as "unknown".

TEMPORAL VARIATIONS IN BREAST CANCER STAGING

The conceptual changes in breast cancer staging implemented over time have accompanied the evolution of scientific knowledge of the disease. The introduction of new

Table 1. Examples of divergences in the process of breast cancer clinical staging, with the respective recommendations.

TNM	Diagnostic question	Specifications	Recommendations
Evaluation of the "T" status	Tumor measurement	cT1 (≤ 2.0 cm) or cT2 (> 2.0 cm) cT2 (≤ 5.0 cm) or cT3 (> 5.0 cm)	Measurement with a caliper Two or more measurements, taken by the same observer Correlation with breast imaging tests
	Presence and extension of tissue involvement (cT4)	Localized (< 1/3 of breast tissue involvement, cT4b) or diffuse (inflammatory carcinoma, cT4d)	Ambient lighting and adequate breast exposure Percentage estimation of tissue involvement Correlation with tissue evaluation in imaging tests Tissue biopsy (punch), in case of doubt
	Chest wall and pectoral muscle involvement	Chest wall involvement (cT4a or cT4c)	Correlation with chest imaging tests (computed tomography and/or magnetic resonance)
Evaluation of the "N" status	Presence and extension of axillary involvement	cN0 (reactive lymph node, free axillary lines) or cN1	Correlation with imaging tests (ultrasound) Ultrasound-guided biopsy of atypical lymph node (fine-needle or core biopsy)
	Affected lymph nodes in the internal mammary, supraclavicular, or infraclavicular chain	cN2 or cN3, depending on the grade	Correlation with imaging tests (ultrasound, magnetic resonance, positron emission tomography-computed tomography – PET-CT) Ultrasound-guided biopsy of atypical lymph node (fine-needle or core biopsy)
Evaluation of the "M" status	Distant metastasis	cM0 or cM1	Correlation with laboratory and/or imaging tests (computed tomography, magnetic resonance, PET-CT) Cytological or histological evaluation (collection of material guided by imaging methods or surgically)

perspectives related to pathologic diagnoses, such as the identification of micrometastasis and isolated tumor cells in axillary lymph nodes, has also forced new concepts to be considered throughout time[24].

In January 2003, with the publication of the 6th edition of the cancer staging manual elaborated by AJCC, patients with affected lymph nodes in the supraclavicular chain were classified as cN3c staging and removed from the cM1 group[3]. Thus, statistics related to metastatic disease collected during this transition phase must be analyzed with caution due to the possibility of selection bias[25].

More recently, in 2018, the 8th edition of the manual removed lobular carcinoma *in situ* from the T*is* staging[26,27], which should affect the incidence curves of the disease in the next years. Reducing the number of T*is* patients might increase the proportion of diagnosed cases in stages II, III, and IV; however, this scenario could reflect an untrue epidemiological event.

Lastly, the situation of patients who achieved complete pathological response (pCR; ypT0ypN0cM0) after neoadjuvant therapies and of those with tumor cells circulating in peripheral blood [cM0(i+)] must be considered. According to the 8th edition of the cancer staging manual, the identification of circulating tumor cells does not classify the patient as cM1 in the absence of other signs of metastatic disease. Similarly, patients with pCR do not constitute a new specific group and remain in the group assigned at the moment of diagnosis. Nevertheless, with advances in the understanding of tumor biology and prognostic stratification of these patients[27,28], new concepts involving pCR and molecular techniques for cancer research might be incorporated into the next editions of breast cancer staging.

BREAST CANCER STAGING: 8TH EDITION

Traditionally, breast cancer staging was based on the anatomical extension of the disease and did not consider tumor biology. After 2018, the new staging (8th edition) elaborated by AJCC included biomarkers for the disease to improve the prognostic stratification of patients[26,27].

This inclusion was based on the retrospective evaluation of patients treated at the MD Anderson Cancer Center, in the USA, and posteriorly validated by the California Cancer Registry[7] and the National Cancer Database[29]. In this context, the inclusion of biomarkers resulted in better accuracy in the patient's prognostic evaluation regarding isolated anatomical staging[7,29].

Anatomical staging (AS) has also changed in relation to the 7th edition but maintains its practical value and remains an adequate instrument for the prognostic evaluation of patients. However, the main change was the creation of the clinical prognostic staging (CPS) and pathological prognostic staging (PPS), with the inclusion of tumor grade, HER2, and estrogen and progesterone receptors.

Genomic signatures can also be used in PPS as a potential modifier of staging, when available and indicated. In these situations, a low-risk genomic result indicates a similar prognosis to stage IA, which can affect the decision-making related to the adjuvant treatment of these women[30,31].

The greatest limitation of this new staging is the wide range of categories according to the combination of different criteria, with more than 1,400 possibilities of clinical staging and prognosis. In some circumstances, the combination of clinical and pathological variables can generate up to four staging classifications for the same patient, from the moment of diagnosis to the postoperative evaluation. These categories can be consulted in several specific tables available at the AJCC website (cancerstaging.org) or other platforms.

In the context of PBCR, the new version of the AJCC makes it even more difficult to collect information regarding breast cancer staging. Therefore, new studies involving this variable should state which type of staging was employed, how and when this assessment was carried out, and lastly, which instrument was used to interpret the obtained TNM. Nevertheless, we recommend caution when comparing studies conducted in different periods and geographic regions, with different or insufficiently described methodologies.

FUTURE PERSPECTIVES

An application developed by a Brazilian mastologist (TNM8 BREAST CANCER CALCULATOR®) was approved and licensed by AJCC for global use and is available at the Apple Store and Google Play at a reasonable price. This application allows the individualized inclusion of variables and automatically provides the corresponding staging[32]. In times of globalization and wide access to information, electronic instruments can help with the data collection process for population-based registries and improve the quality of information on breast cancer staging.

Finally, we emphasize the need for continuing education, along with constant training for all professionals involved in the breast cancer epidemiological context, from assistant medical doctors to the professionals responsible for gathering and registering this information. The utilization of new technologies can help standardize the information and reduce the divergences related to cancer staging registry.

AUTHORS' CONTRIBUTIONS

L.R.S.: Conceptualization, data curation, formal analysis, writing — original draft; M.P.C.: Formal analysis, writing — original draft; R.F.-J.: Formal analysis, writing — original draft.

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IMAGES IN MASTOLOGY
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Recurrent diffuse large B-cell lymphoma mimicking primary breast cancer

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ABSTRACT

Breast lymphoma can represent 0.8%–2.2% of extranodal lymphomas and 0.1%–0.5% of primary breast neoplasms. Imaging findings are not specific, and its distinction from primary invasive breast carcinoma should be based on clinical data and histopathological analysis. We present the case of a 62-year-old woman who showed an unusual pattern of recurrent diffuse large B-cell lymphoma (DLBCL) mimicking primary breast cancer on imaging studies, including mammography, ultrasound, magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT).

KEYWORDS: Breast neoplasms; Lymphoma; Mammography; Ultrasonography; Magnetic resonance imaging; PET-CT.

A 62-year-old woman presented to our hospital with a left breast lump. She had a prior history of non-Hodgkin's lymphoma treated with chemotherapy, in remission for two years. Mammography (Figure 1A), ultrasound (Figure 1B), and magnetic resonance imaging (MRI) (Figure 2) showed an irregular mass in the upper quadrants of the left breast with ipsilateral axillary lymph node enlargement. Ultrasound-guided core-needle biopsy of the breast mass and axillary lymph nodes was compatible with recurrent diffuse large B-cell lymphoma (DLBCL). Immunohistochemistry showed positive expression of CD20, CD79a, CD5, Bcl-6, Bcl-2, and MUM1; negative expression of CD3, CD10, CD23, Cyclin D1, CD30, EBV, and C-MYC; and 90% expression of Ki-67. Whole-body positron emission tomography-computed tomography (PET-CT) was performed and showed no other sites of disease (Figure 3).

Breast lymphoma can represent 0.8%–2.2% of extranodal lymphomas and 0.1%–0.5% of primary breast neoplasms. The most common subtypes of breast lymphoma originate from B-cells, including DLBCL, marginal zone lymphoma (MALT lymphoma), and follicular lymphoma. Age at diagnosis usually ranges from 55 to 65 years, and the most frequent clinical presentation is a breast lump that may be associated with pain in 25% of cases. Ipsilateral axillary lymph node involvement can occur in more than 40% of cases.[1,2] Imaging findings are not specific, and its distinction from primary invasive breast carcinoma should be based on clinical data and histopathological analysis.[3,4] At mammography, they usually present as single or multiple masses, which may be bilateral in about 28% of cases; spiculated margins,

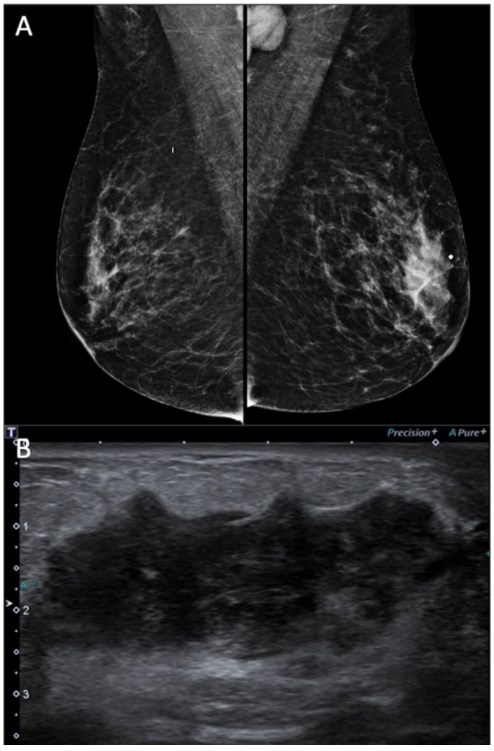

Figure 1. Bilateral mammography on mediolateral oblique (MLO) view (A) showed an irregular hyperdense mass in the upper quadrants of the left breast, near the metallic marker in the left breast lump, and left axillary lymph node enlargement. Ultrasound (B) revealed an irregular hypoechoic mass in the left breast with posterior acoustic enhancement.

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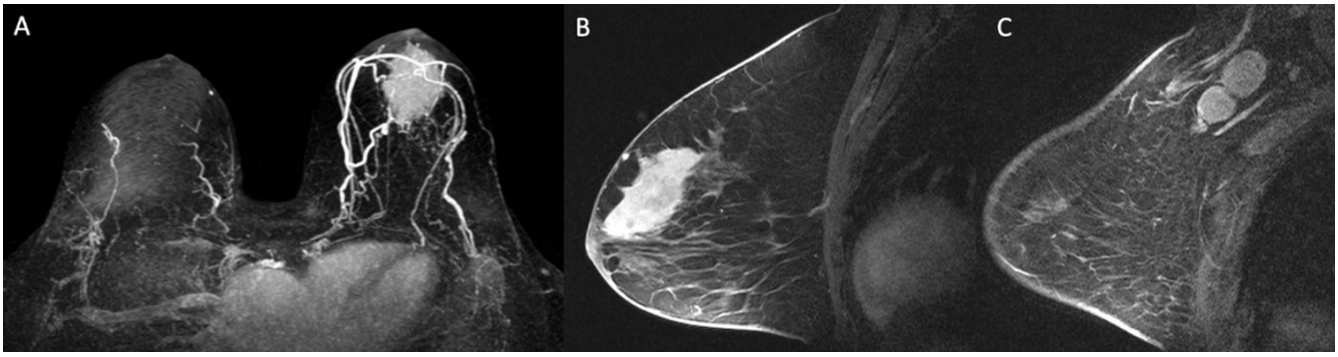

Figure 2. Breast magnetic resonance imaging (A: axial 3D MIP subtraction image; B, C: sagittal T1-weighted enhanced images) showed an irregular mass in the upper quadrants of the left breast (A and B) and left axillary lymph node enlargement (C).

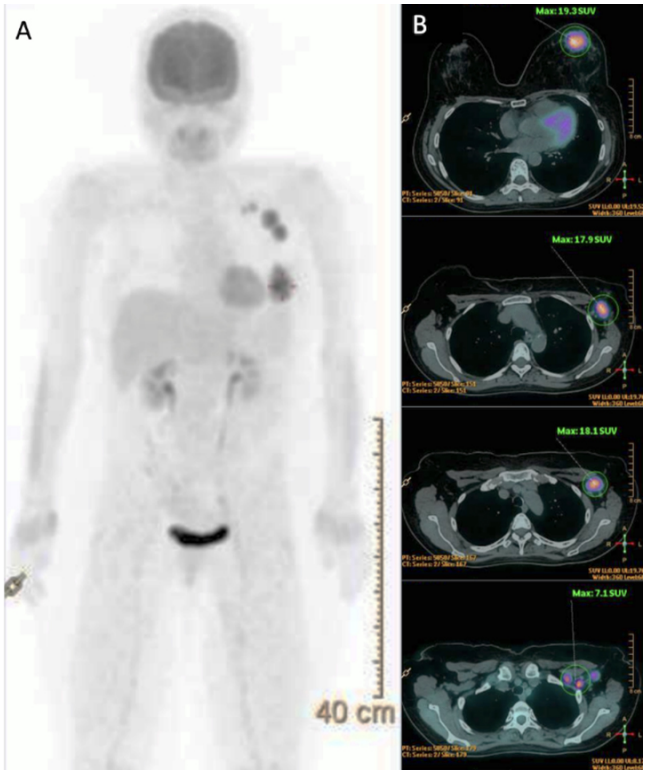

Figure 3. Whole-body positron emission tomography-computed tomography (PET-CT) (A: coronal 3D MIP PET image; B: axial fused PET-CT images) revealed a hypermetabolic mass in the left breast (SUVmax: 19.3) and left axillary lymph node enlargement at levels I and II (SUVmax: 18.1).

calcifications, and architectural distortion are unusual and suggest primary breast cancer. At ultrasonography, they frequently present as a hypo- or anechoic mass with indistinct or circumscribed margins, posterior enhancement, or no posterior features. At MRI, breast lymphoma most often appears as an irregular or circumscribed mass with mild heterogeneous internal enhancement, usually presenting a plateau or washout kinetic curve and restricted diffusion. Breast MRI can provide greater sensitivity in detecting multifocal and/or multicentric diseases.[5] Whole-body PET-CT can contribute to distant staging due to its high sensitivity and specificity in this entity, being also useful in evaluating the therapeutic response.[6]

This case showed an unusual pattern of recurrent DLBCL mimicking primary breast cancer. Immunohistochemical analysis revealed expression of CD5 and high expression of Ki-67, which is typically associated with aggressive clinical features and adverse outcomes. The patient presented complete response on PET-CT after treatment with rituximab and ifosfamide, carboplatin, and etoposide ICE (R-ICE) chemotherapy, in addition to autologous stem cell transplantation.

AUTHORS' CONTRIBUTION

D.C.D.: investigation, writing – original draft, writing – review & editing. E.N.P.L.: investigation, writing – review & editing. A.G.V.B.: investigation, writing – original draft, writing – review & editing. P.N.V.P.B.: conceptualization, investigation, supervision, writing – review & editing.

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IMAGES IN MASTOLOGY
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Ulcerative-vegetative Locally Advanced Breast Carcinoma Mimicking Flower Image

René Aloisio da Costa Vieira[1,2,3], Idam de Oliveira-Junior[1,4]

Ulcerated locally advanced breast carcinoma (LABC)[1,2] is an uncommon topic in the literature. Several factors contribute to delayed diagnosis, such as the health system, factors related to the patient (lack of knowledge, fear and denial of the disease), in addition to rapid tumor growth.

Ulcerated tumors can occur in any breast location, including in areolar Paget's disease[3]. They are usually high histologic-grade tumors, high Ki67 index and triple negative breast cancer (TNBC) molecular subtype with lymph node involvement[2]. There are disagreements about the simple presence of ulceration determining worsening of patient's prognosis[1,2].

An ulcerated lesion leads to bleeding and may be the gateway to secondary infection. In this context, surgery can be[4-6]:

- up-front hygiene (avoids bleeding and infection, but is associated with the need for local flaps);
- elective, after neoadjuvant chemotherapy treatment (leaves the patient vulnerable to infection and sepsis[7], regardless of neutropenia);
- elective, after radiotherapy, in extreme situations[8] (attempt to increase resectability).

Prior to surgery, a surgical wound culture can be performed to guide the choice of antibiotic therapy. During surgery, special care must be taken (covering the exposed area with compresses and administration of broad-spectrum antibiotic for therapeutic purposes)[9].

A 52-year-old female, rural worker, complaining of a tumor in the right breast for four months. She had LABC, T4bN3 (infraclavicular – IFV on tomography) M0, "*peau d'orange*" measuring 19 x 15 cm, with a 15 x 10 cm ulcerated vegetative lesion in the right breast (Figure 1). Pathological examination revealed an invasive ductal carcinoma, nuclear and histological grade 3, Ki67 index of 50%, TNBC. We opted for primary surgical treatment, with isolation of ulcerated area (Figure 2) and antibiotic therapy, followed by modified radical mastectomy associated with rotation of the ipsilateral thoracoabdominal dermomat flap (ITADE)[10]. No surgical

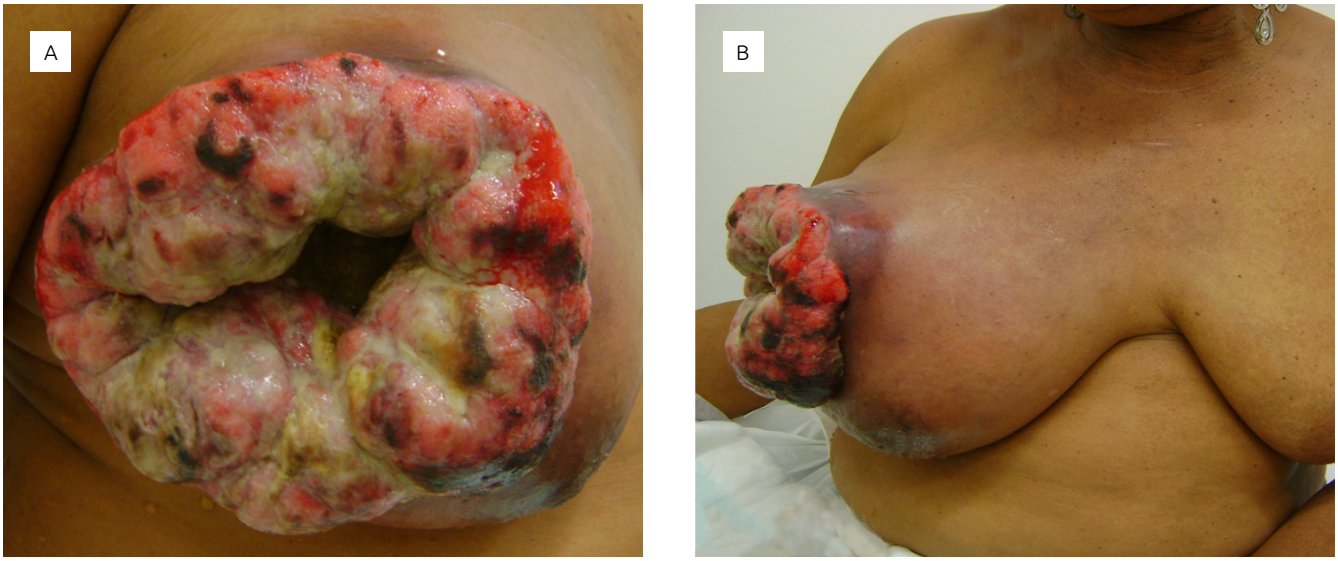

Figure 1. Ulcerative-vegetative locally advanced breast neoplasm. (A) front view; (B) side view.

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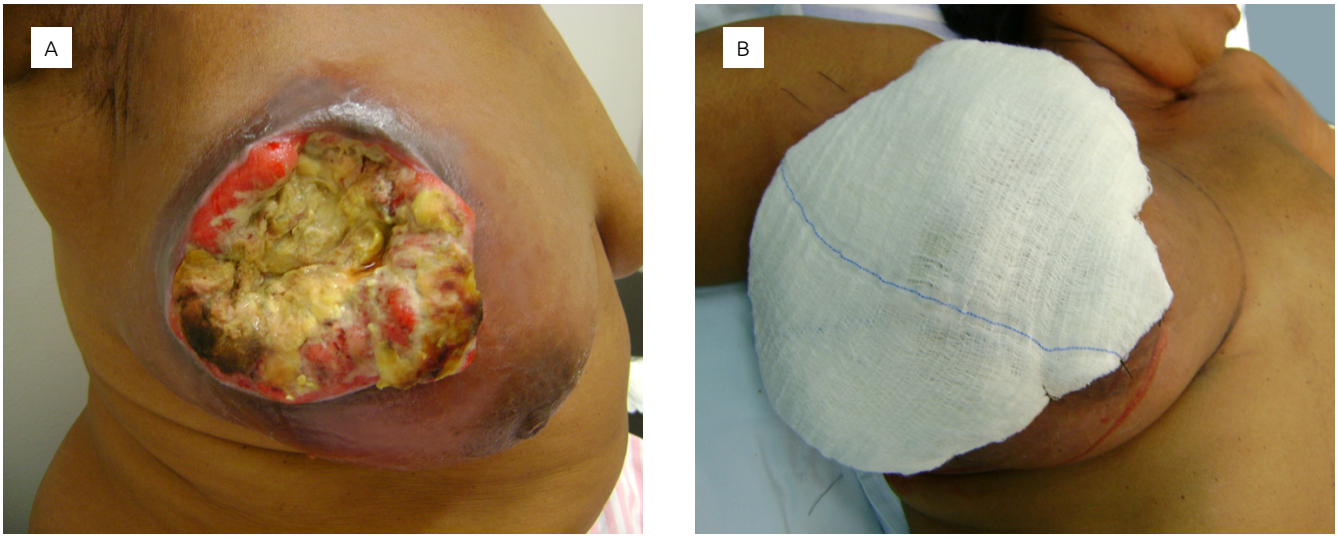

Figure 2. Perioperative. (A) Spontaneous necrosis and disappearance of vegetative lesion; (B) surgical wound dressing.

complications were seen. Pathological examination showed an 18 cm tumor and 4/22 compromised lymph nodes. No postoperative complications occurred. The patient then received adjuvant chemotherapy (AC-T scheme) and radiotherapy (plastron, armpit and supraclavicular fossa). Currently, after 10 years of follow-up, she is alive and without evidence of oncological disease.

The image has different characteristics compared to other ulcerated lesions, as it assumes an ulcer-vegetative aspect, resembling a "flower", the red gerbera with a blackened center. Symmetrical vegetative tumor tissue is observed around an ulcerated and necrotic central axis, which justifies this rare presentation. An image of balanced symmetry that starts from a central axis is often seen in nature, but not in the presentation of breast cancer.

AUTHORS' CONTRIBUTION

R.A.C.V.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. I.O.J.: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

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LETTER TO THE EDITOR
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Nipple-sparing mastectomy in normal breast: consequence of simulation and disease anxiety

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ABSTRACT

Diagnosis in psychiatry is a thorough and potentially artificial process. In this letter, we discuss this diagnostic process in the context of a young patient who underwent nipple-sparing mastectomy after falsifying a breast biopsy report revealing invasive ductal carcinoma. The secondary pathology revision was also forged by the patient and confirmed the diagnosis. The patient was summoned by the Service's board and admitted the falsification of breast cancer reports. After evaluation at the Psychiatric Service, changes in vital mood, psychosis, delusional activity and obsessive-compulsive symptoms were ruled out. In view of the growing demand for prophylactic mastectomy observed worldwide, similar cases may become more frequent.

KEYWORDS: breast neoplasms; patient simulation; factitious disorders.

Dear editor,

We would like to report a case received for evaluation in our Service, relevant for its severity, rarity and for having drawn multidisciplinary attention. In addition, the present case exposes the detailed and artificial diagnostic process in psychiatry. In this case, identifying the real motivation for fraud determines the final diagnosis.

A 24-year-old woman was sent to the Mastology Service after falsifying a breast biopsy report, revealing an invasive ductal carcinoma. The patient also forged the secondary pathology revision and confirmed the diagnosis. She underwent nipple-sparing mastectomy associated with sentinel lymph node biopsy and immediate right breast reconstruction with expansive prosthesis. After extensive evaluation of the material, fibrocystic alterations and fibroadenosis areas were observed, with no evidence of neoplasm. The patient was summoned by the Service board and admitted the forgery of the reports regarding the breast cancer.

After evaluation in the Psychiatry Service, vital mood alterations, psychosis, delusional activity and obsessive-compulsive symptoms were ruled out. The patient pointed out as motivation for her actions the fact that she had lost her grandfather to prostate cancer a year before, having then acquired an excessive fear of developing neoplasms in the future. Upon discovering the nodules, the patient aimed for the removal of the breast. For that matter, the patient admitted feeling regretful for breaking the law, but not for the surgical removal of her breast.

In the case described above, the diagnosis established was disease anxiety, by DSM-5. Nonetheless, the simulation attestation is also adequate, once there is conscious and deliberate production of the symptoms, and equally conscious motivation by the examinee[1]. However, while interviewing the patient's mother, it was ascertained that the patient was recently divorced and that, at the time of the surgery, the marriage was about to end. It was observed from these factors the presence of a distinct unconscious motivation: through the production of a mammary disease, she would be able to draw more attention from her ex-husband, and even a possible way of keeping the marriage. The patient denies this hypothesis and the analysis of this possible unconscious factor would demand extensive anamnestic and therapeutic processes. Nevertheless, in case this version is true, the most adequate diagnosis by the DSM-5 would be Factitious Disorder, once there is conscious production of the act and unconscious motivation[1].

To our knowledge, this is the second case of effectively performed mastectomy after the adulterated production of reports[2].

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Notwithstanding, other cases of simulation have been described involving mammary pathologies and fictitious breast cancer family history[3,4]. Therefore, because of the increasing demand for prophylactic mastectomy observed all over the world, similar cases might become more frequent.

AUTHORS' CONTRIBUTIONS

L.R.S.: Conceptualization, Data curations, Formal analysis, Writing — original draft, Writing — review & editing.

S.A.T.S.: Conceptualization, Data curations, Formal analysis, Writing — original draft, Writing — review & editing.

M.F.C.: Conceptualization, Data curations, Formal analysis, Writing — original draft, Writing — review & editing.

G.A.M.: Data curations, Writing — original draft, Writing — review & editing.

M.A.R.M.: Data curations, Formal analysis, Writing — original draft, Writing — review & editing.

R.F.J.: Conceptualization, Data curations, Formal analysis, Writing — original draft, Writing — review & editing.

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OBITUARY
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Benedito Borges da Silva

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Professor Benedito Borges da Silva, MD, PhD, was born on March 20, 1950. Graduated in Medicine at Universidade Federal do Piauí (UFPI) in 1976. He completed his Doctorate in Medicine (Gynecology) at Universidade Federal de São Paulo (UNIFESP) in 1997, and Post-doctorate at Universidade Estadual de Campinas (UNICAMP) (2002). He was a Full Professor of the Maternal and Child Department (Gynecology) at the UFPI and worked for their Voluntary Service Program during his postgraduate studies. He was a master's and doctoral advisor at the Graduate Program in Science and Health of UFPI and in Biotechnology (Graduate Program in Biodiversity, PPGB) in the Northeast Biotechnology Network (RENORBIO). He was a 1B Research Productivity Fellow and Ad Hoc Consultant to the National Council for Scientific and Technological Development (CNPq), a founding member of the Piauí Academy of Sciences (2002), and President of the Piauí Society of Gynecology and Obstetrics (1991–1993). Executive Coordinator of the Medical Residency Program at the Health Sciences Center (CCS) at UFPI (1997–1999). Coordinator of the discipline of Gynecology at UFPI (2001–2015). Head of the CCS Maternal and Child Department (2000–2002). Coordinator of the Gynecology Clinic at Hospital Getúlio Vargas (HGV) (2001–2013). Coordinator of the Interinstitutional Master's at UFPI–UNICAMP (2000–2003). Director-General of the Getúlio Vargas Hospital, in Teresina, Piauí (2003). Coordinator of Medical Residency in Mastology at UFPI (2005–2014). President of the Research and Bioethics Commission of the Brazilian School of Mastology (2011–2013). Member of the National Specialized Committee on Mastology of FEBRASGO (2012–2015). Coordinator of the Master's in Science and Health (2009–2010 and 2012–2016). PhD coordinator, member of the Scientific Committee and leader of a study and research group in Gynecological and Breast Oncology

at RENORBIO, Ponto Focal Piauí (2007–2010). He has published over 100 full-length articles in indexed international journals, and has three computer programs registered with the National Institute of Industrial Property. He has also been the advisor of 121 works, being 49 masters, 14 doctorates, 43 scientific initiations, 7 specializations and 8 of a different nature. He has acted in Medicine with an emphasis on Gynecology and Mastology, and passed away of complications from COVID-19 on September 6, 2021.

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ERRATUM
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In the manuscript "The first mastectomy: truth or legend?", DOI: 10.29289/25945394202020200063, published in the Mastology 2020;30:e20200063, on page 1:

Where it reads:

In 1984, Halsted published the 50 cases that he operated with a recurrence rate of 6%, while in Europe the recurrence rate were from 51% to 82%, because they did not use the surgical technique described by Halsted.

It should read:

In 1894, Halsted published the 50 cases that he operated with a recurrence rate of 6%, while in Europe the recurrence rate were from 51% to 82%, because they did not use the surgical technique described by Halsted.

ERRATUM
https://doi.org/10.29289/259453942020V30S1027ERRATUM

In the abstract "Gestational Gigantomastia", DOI: 10.29289/259453942020V30S1027, published in the Mastology 2020;30(Suppl 1):27:

Where it reads:
Letícia Augusto Garcia[1]

It should read:
Letícia Augusto Garcia[1], Vicente Tarricone Júnior[1], Marco Antônio Dugatto[1], Lara Varini Soares[1], Fabiano Affonso Kimus[1]

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