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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

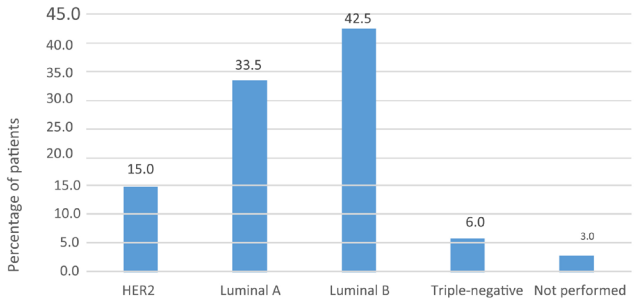
The sample consisted of 34 women under 50 years of age diagnosed with breast cancer, treated at the Hospital do Câncer de Franca from January 2015 to February 2018.

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.



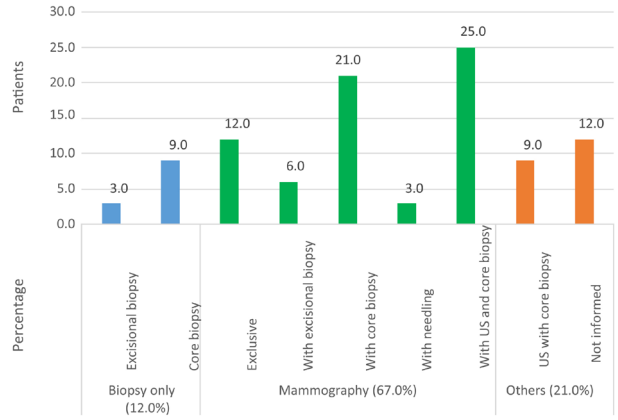
Graph 1. Percentage of patients according to tumor subtype.

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

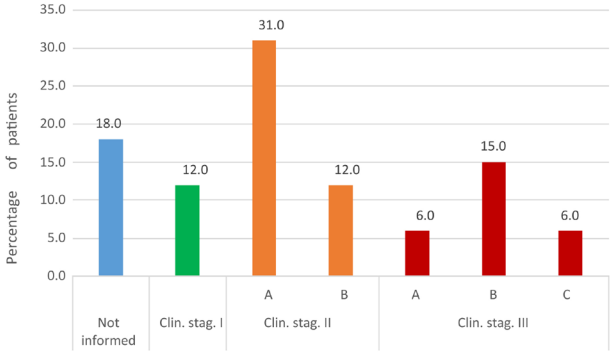
Table 2. Mammographic BI-RADS in the first appointment.

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



US: ultrasound.

Graph 2. Complementary diagnostic tests performed (%).



Clin. stag.: Clinical staging.

Graph 3. Clinical staging of patients (%).

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).

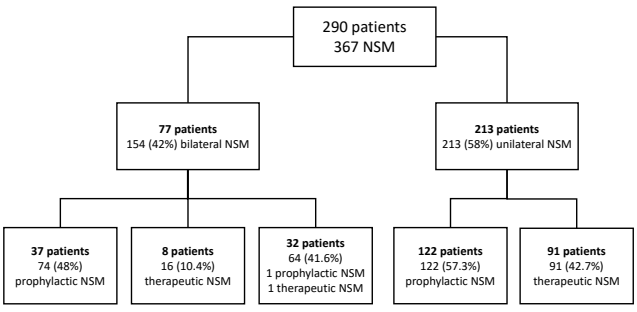

Figure 1. Number of patients and nipple-sparing mastectomies (NSM) performed at A.C. Camargo Cancer Center between January 2007 and December 2017.

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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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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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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ORIGINAL ARTICLE
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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

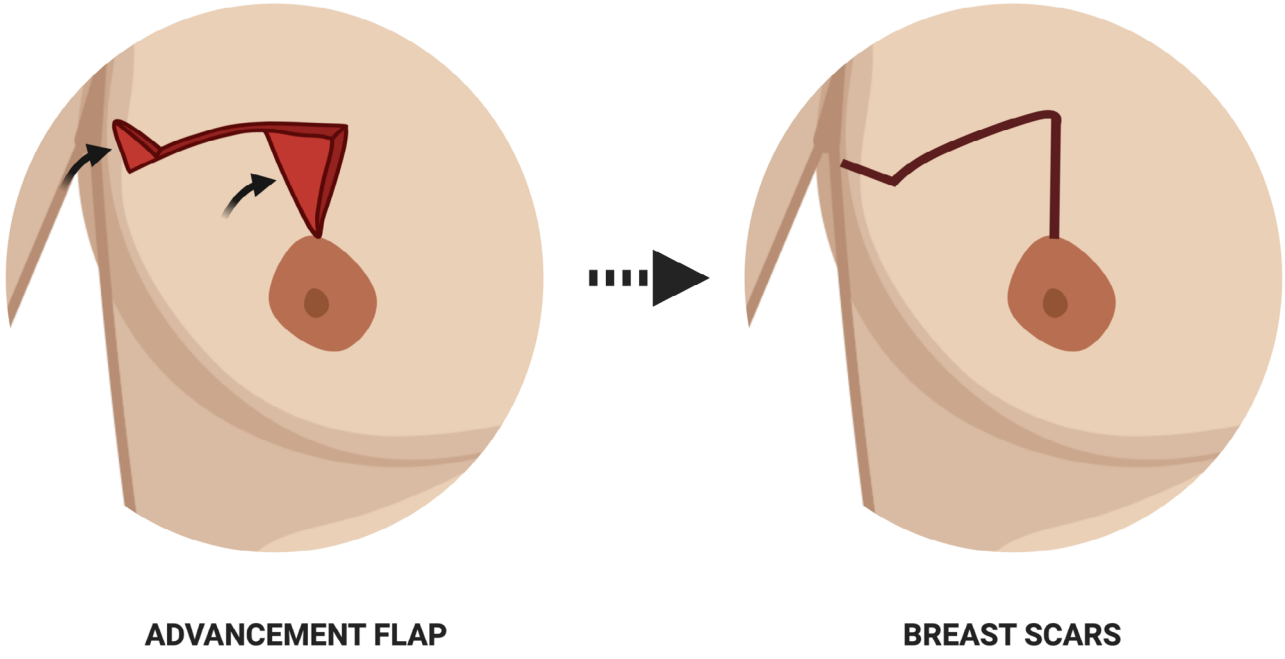

Figure 1. Schema of breast advancement flap after a triangular resection and a small upside-down "Burow" triangle to allow skin compensation in the axillary region.

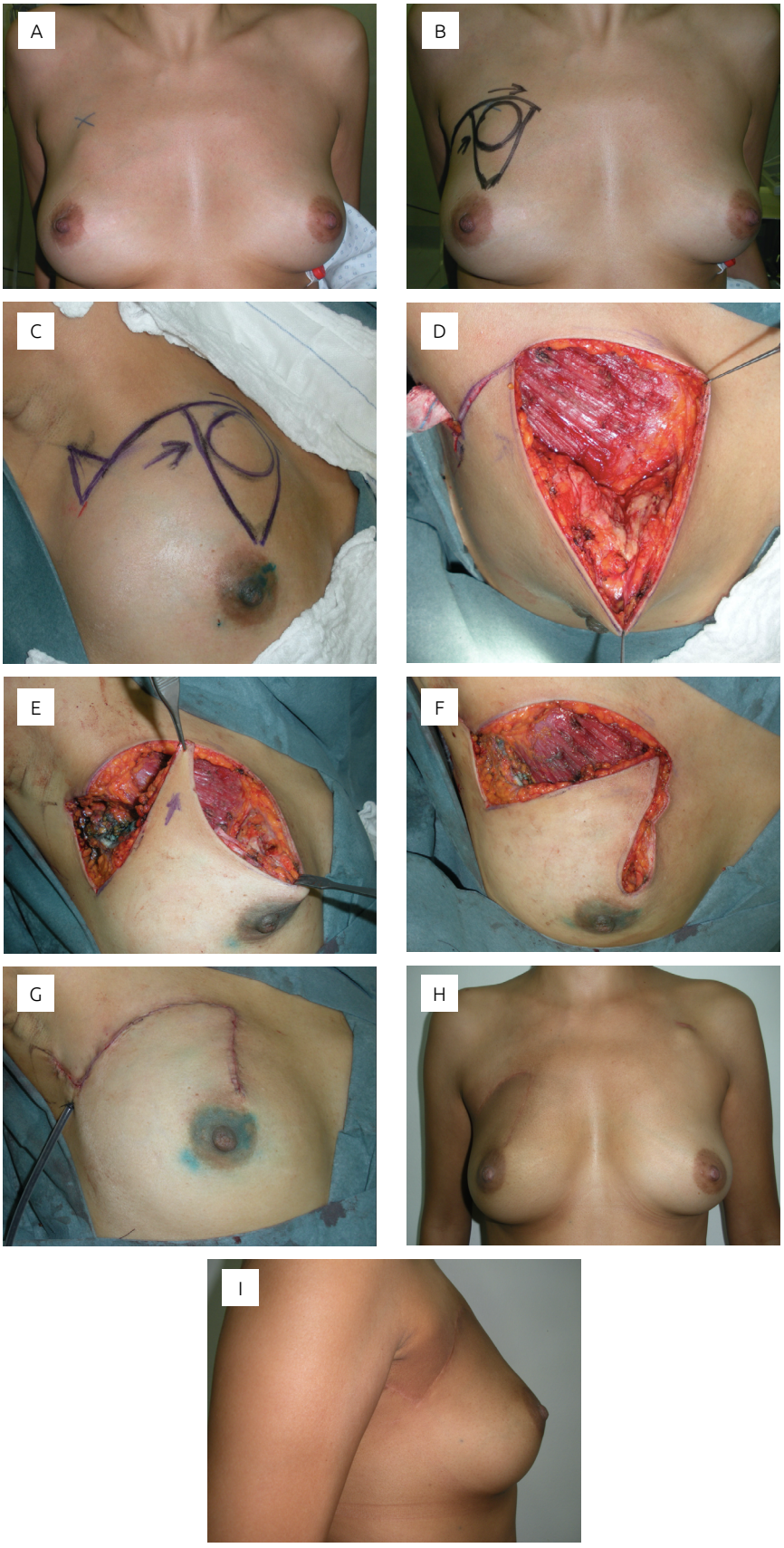

Figure 2. 37-year-old patient. 3.5-cm luminal A invasive ductal carcinoma, located 10 cm from the sternal notch. Triangular quadrantectomy (90 g) with negative SLNB* (A–D). Lateral glandular matrix rotation to cover the breast defect (E–G). 4-year follow-up pictures (H and I) with symmetrical breast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

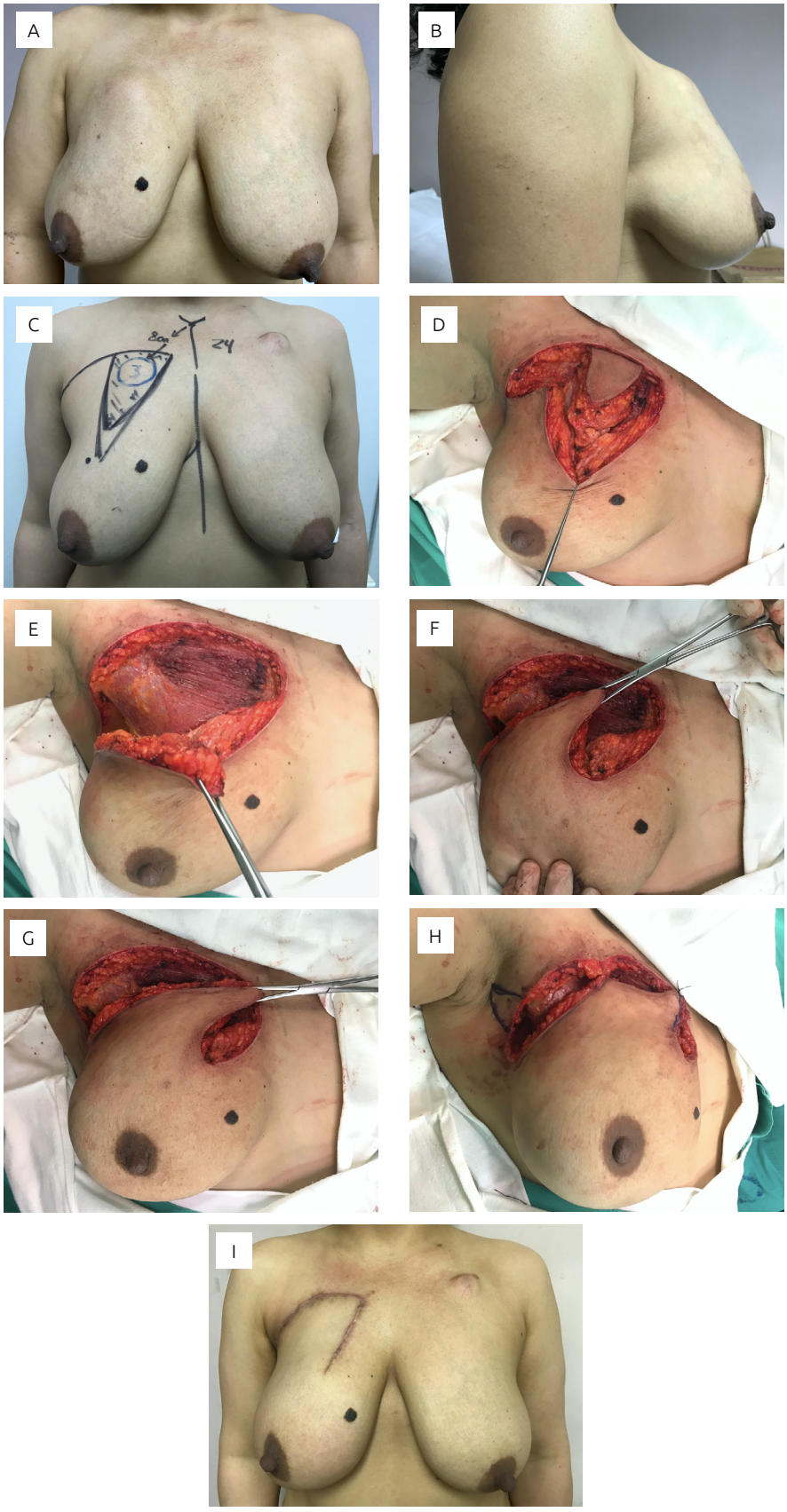

Figure 3. 34-year-old patient. 5-cm triple-negative invasive ductal carcinoma (IDC). (A, B) T3N2M0 neoadjuvant chemotherapy with adequate response to anthracycline regimen but progression with taxanes. (C–E) Large breast resection, including skin and a superficial layer of the pectoral muscle (65 g). 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.
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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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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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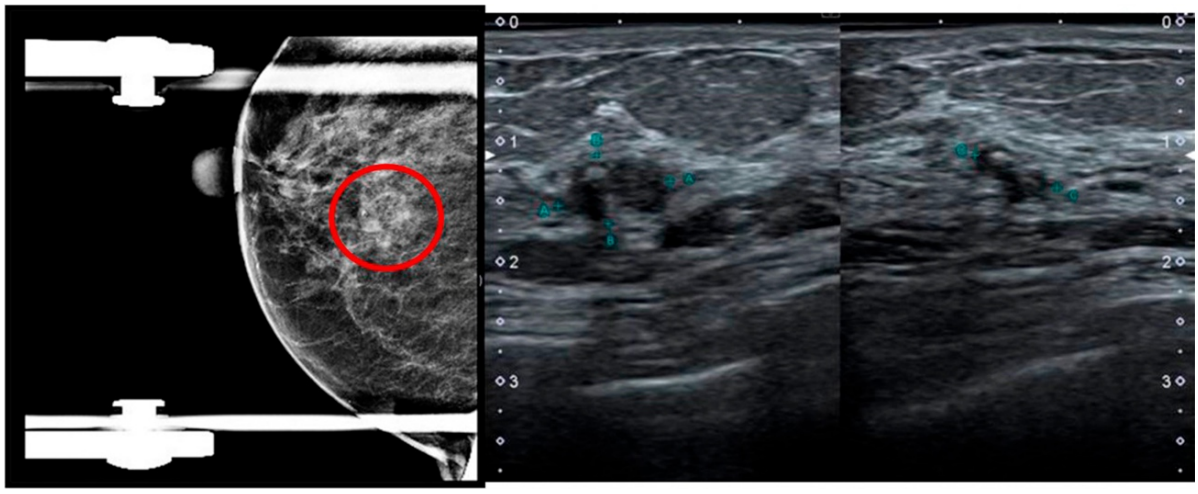

Figure 1. Mammography (left) and ultrasound (right) demonstrating a 9 mm hypoechoic and irregular nodule in the lower internal quadrant of the right breast.

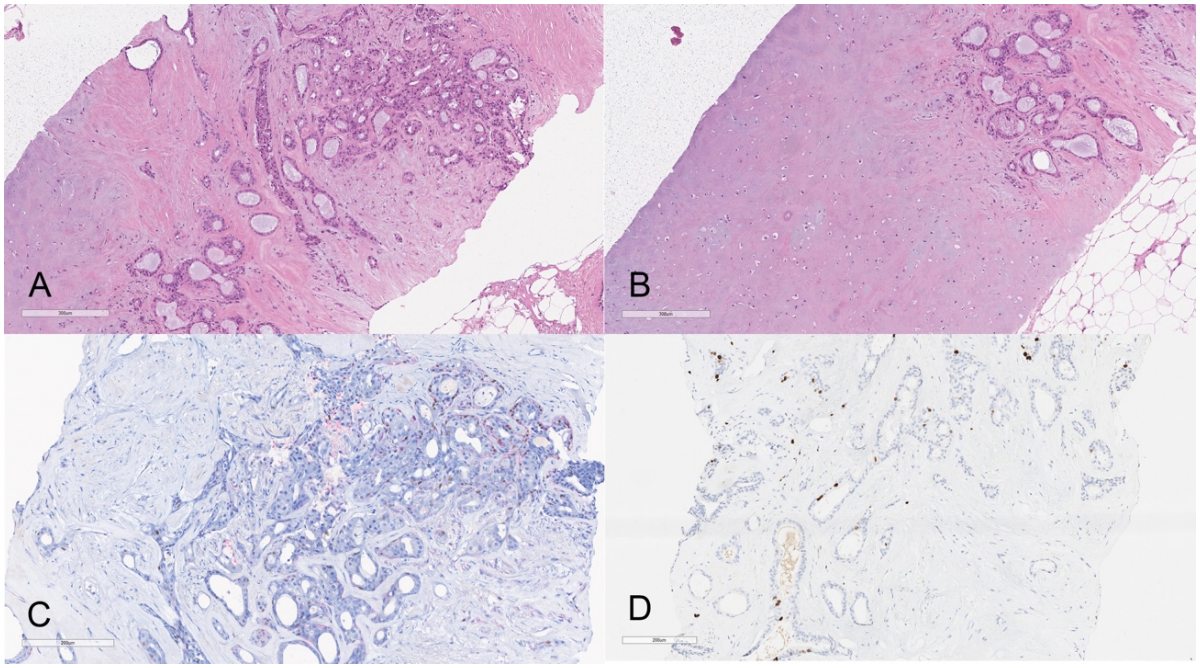

Figure 2. Hematoxylin-eosin stain (100x) of core-needle biopsy specimen of (A) the right breast lump showing glands surrounded by epithelial and myoepithelial cells and (B) focus of chondromyxoid stroma. Immunohistochemical (100x) of core-needle biopsy specimen of the right breast lump showing positivity for p63 (nuclear) and (C) calponin (cytoplasmatic) expression in myoepithelial cells and (D) low Ki67 proliferation rate.

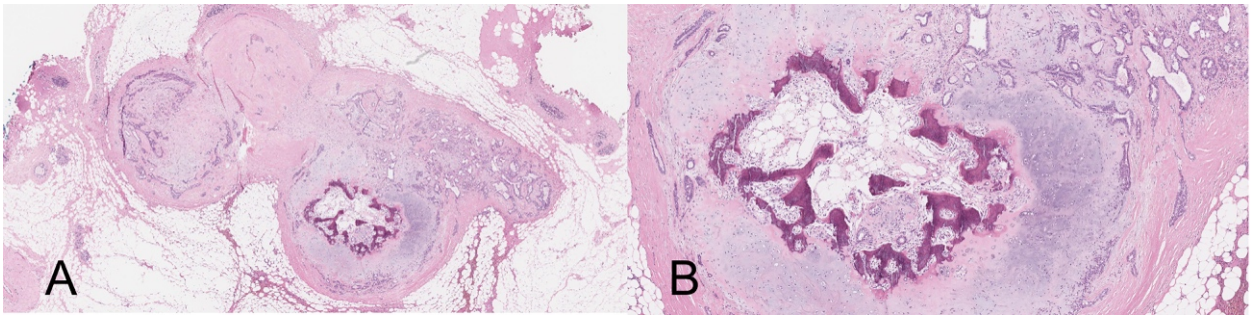

Figure 3. (A) Hematoxylin-eosin stain of surgical specimen showing a well-defined lesion under low-power magnification (40x) and (B) a high-power magnification (200x) of pleomorphic adenoma with glandular elements in chondromyxoid stroma with cartilaginous and osseous metaplasia.

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

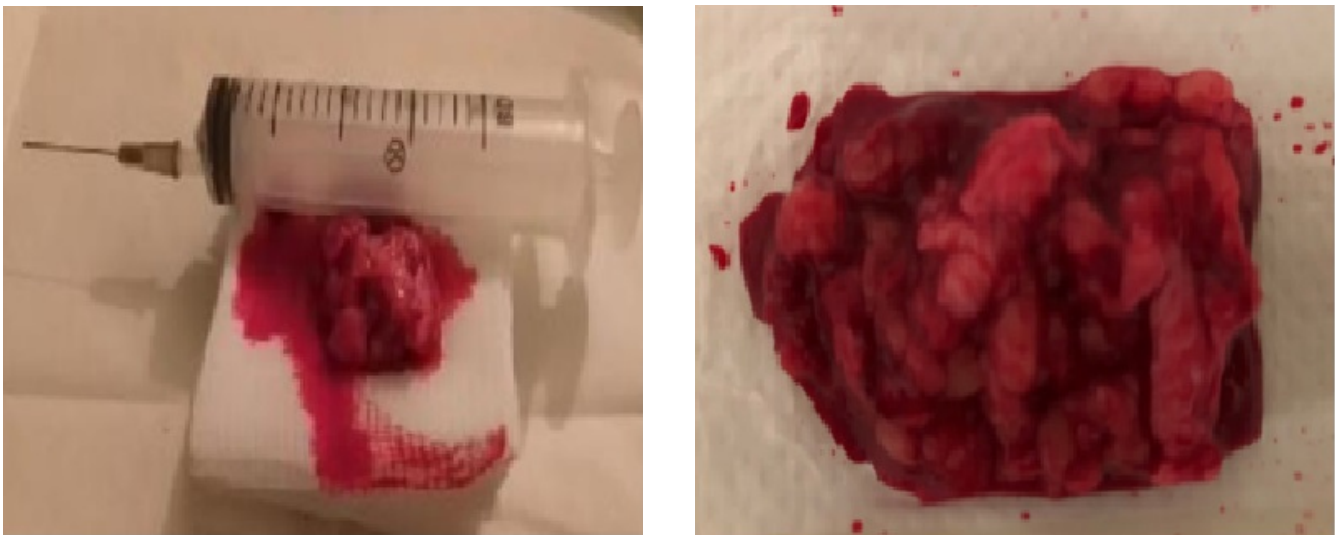

Figure 2. Ultrasound-guided vacuum-assisted excision of gynecomastia: surgical specimen.

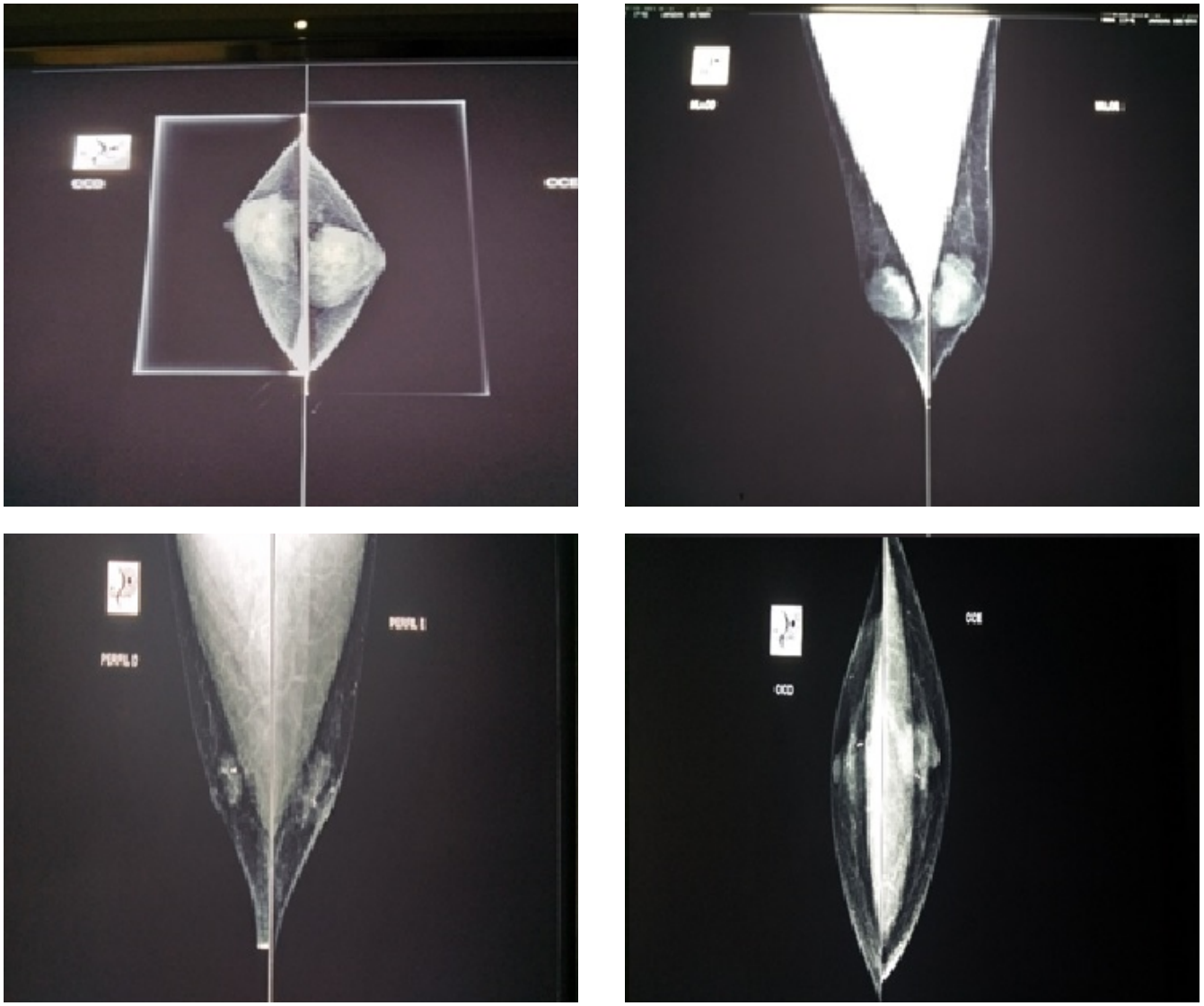

Figure 3. Mammograms before and six months after ultrasound-guided vacuum-assisted excision of gynecomastia.

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

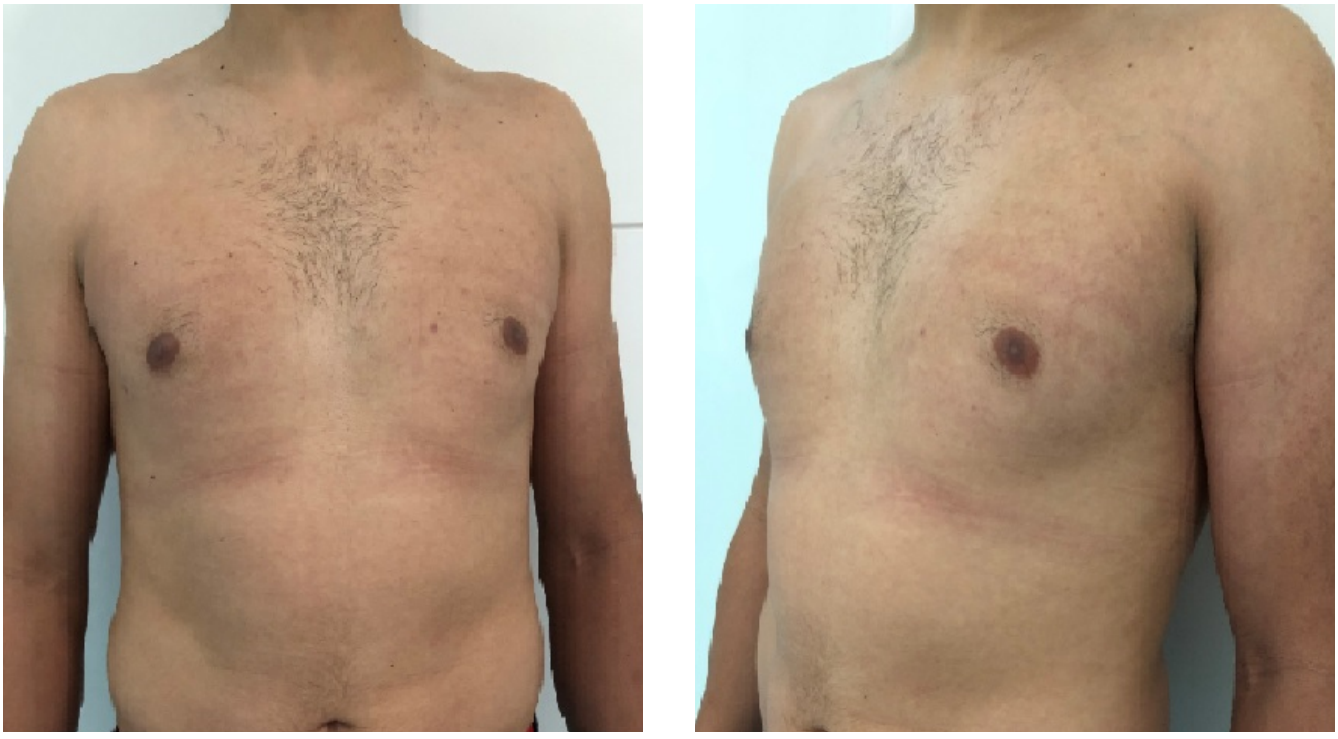

Figure 4. 34-year-old man with Simon grade 2 gynecomastia.

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

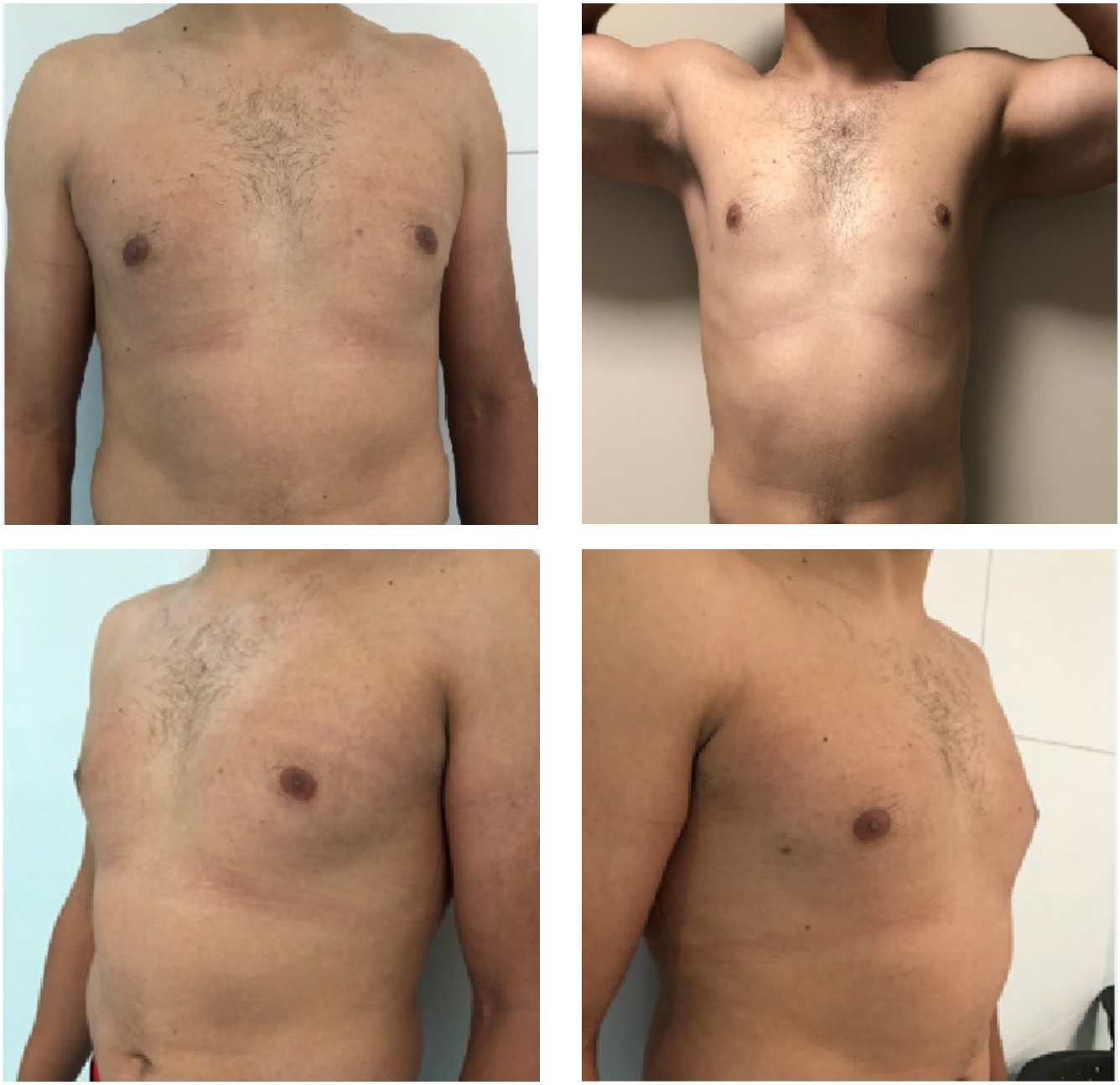

Figure 5. Same patient six months after ultrasound-guided vacuum-assisted excision of gynecomastia.

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

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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".

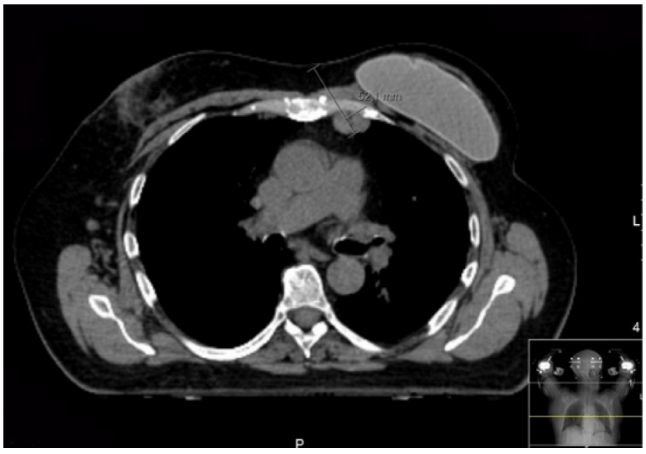

Figure 1. Planning computed tomography scan prior to radiotherapy (coronal plan): lymphadenopathy of the internal mammary lymph nodes on the left side.

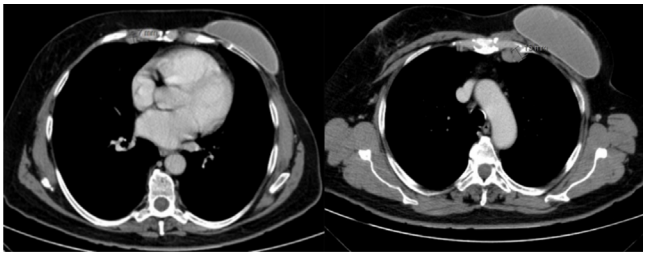

Figure 2. Contrast computed tomography scan (coronal plan): lymph nodes in both internal mammary chains, the biggest one on the left side with 15 mm.

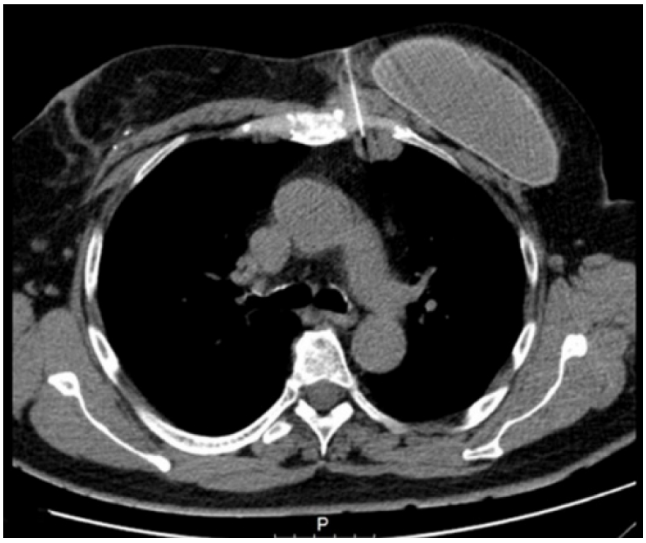

Figure 3. Core needle biopsy of the suspicious lymphadenopathy.

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].

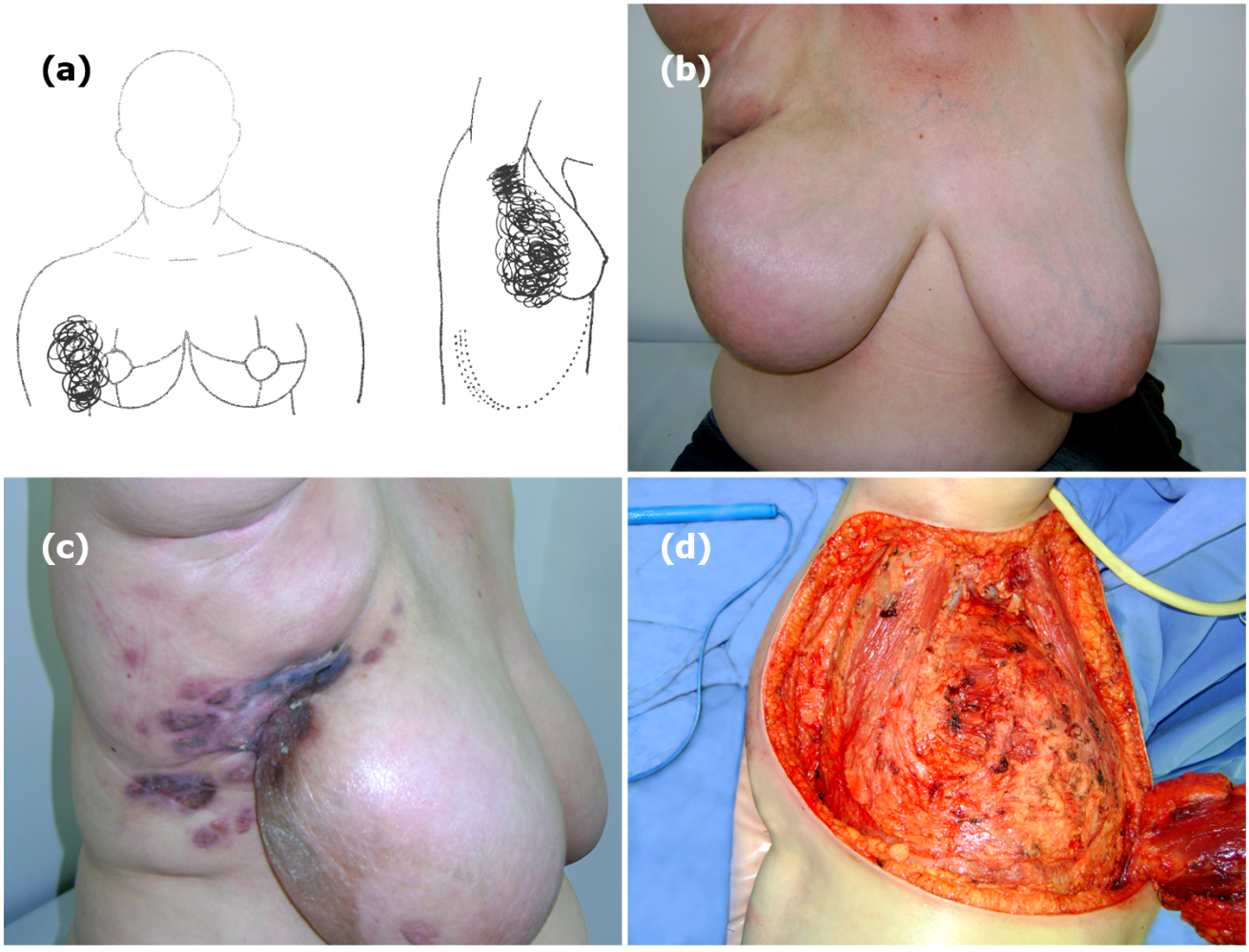

Figure 1. (A) Schematic representation prior to treatment; (B) control after neoadjuvant chemotherapy; (C) resection area; (D) resected area.

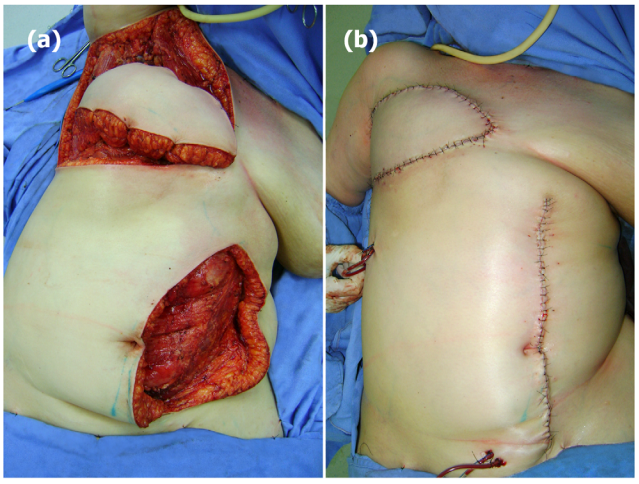

Figure 2. Vertical rectus abdominis flap. (A) Fabrication of the flap and transposition to the axillary region. Observe the use of zone I of the flap only. (B) Surgical result.

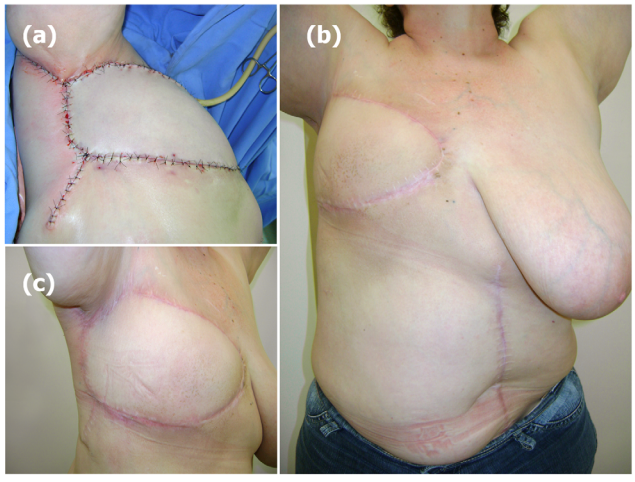

Figure 3. Vertical rectus abdominis flap: flap coverage area, with local healing and final result. (A) Intra-operative; (B and C) postoperative.

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.

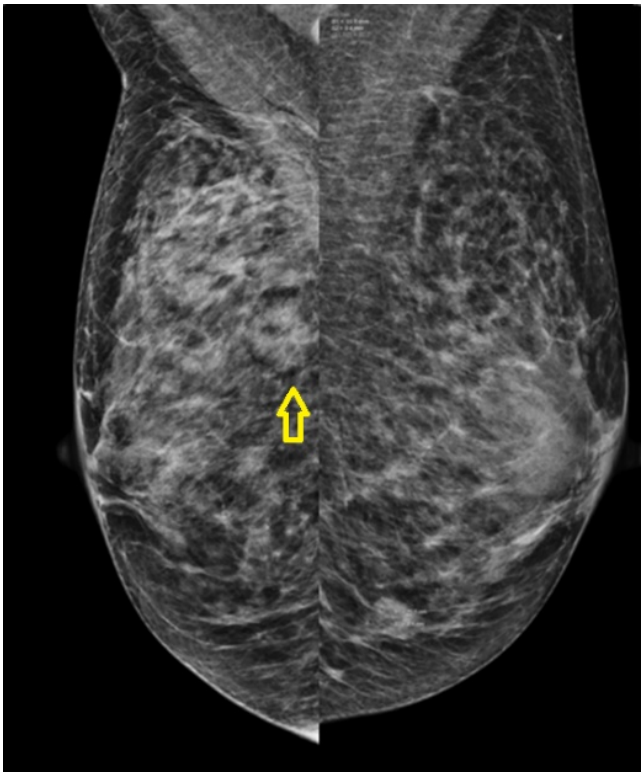

Figure 1. Mammography in oblique mediolateral view showing a nodule in the right breast, measuring 2 cm, at the junction of the lateral quadrants, oval, with indistinct margins (BI-RADS 4A).

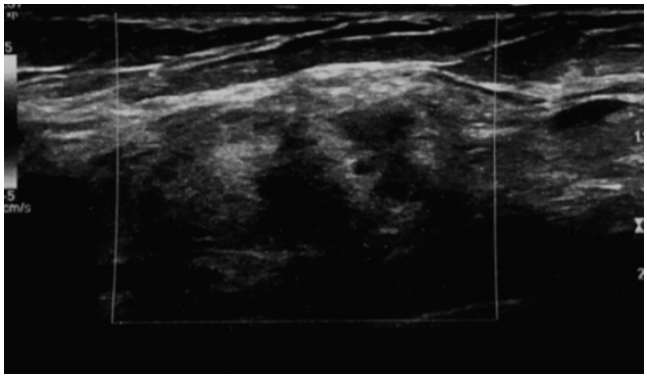

Figure 2. Ultrasonography showing an oval nodule, parallel to the skin, circumscribed, heterogeneous, without flow to the color Doppler study, at the union of the lateral quadrants, at 9 am, 4 cm apart from the papilla, measuring 2 × 1.4 × 1.8 cm.

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,

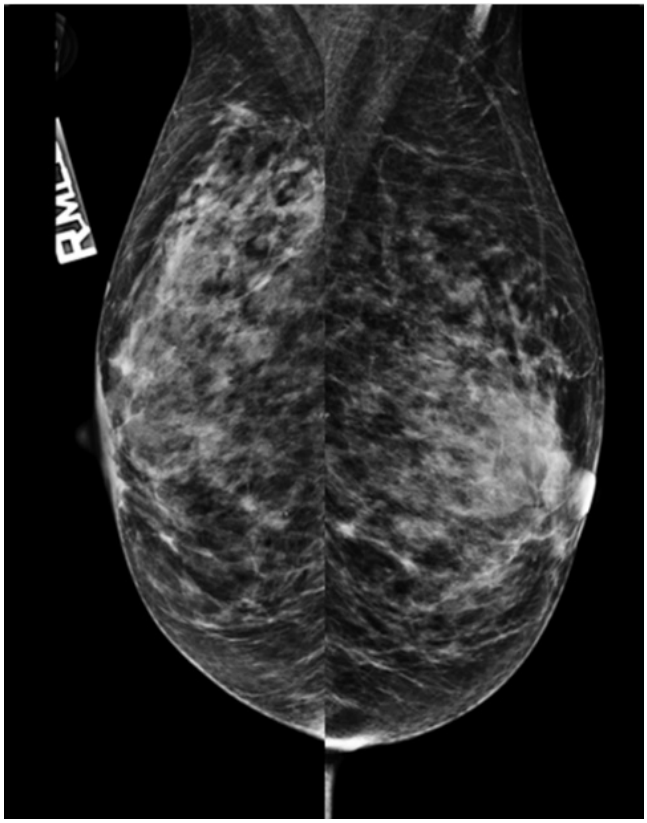

Figure 3. Mammography performed after 3 cycles of chemotherapy no longer demonstrated the nodule.

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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SHORT COMMUNICATION
https://doi.org/10.29289/2594539420200067

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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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.
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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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ERRATUM
https://doi.org/10.29289/25945394202020200063ERRATUM

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.