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Praça Floriano, 55, sala 801, Centro – 20031-050 – Rio de Janeiro (RJ)
Phone number: (21) 97271-0192
E-mail: secretaria@sbmastologia.com.br

ABOUT

Founder: Antônio Figueira Filho

Submissions - mailing address: Praça Floriano, 55, sala 801, Centro – Rio de Janeiro (RJ) – 20031-050

National and international subscription and advertising: Sociedade Brasileira de Mastologia - Phone number: (21) 97271-0192

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Neuromuscular bandage for the prevention of post-mastectomy seroma: a clinical trial protocol

Erica Alves Nogueira Fabro[1,*], Rejane Medeiros Costa[1], Flávia Oliveira Macedo[1], Daniele Medeiros Torres[1], Suzana Sales de Aguiar[1], Luiz Claudio Santos Thuler[2], Anke Bergmann[2]

ABSTRACT

Introduction: Seroma is the most common early complication after breast cancer surgery and is associated with other complications and adjuvant therapy delays. A potential hypothesis for its prevention is the obliteration of dead space between tissues, which can be achieved by external compression. To assess whether the use of a neuromuscular bandage employing the compressive technique during the first postoperative week is effective in preventing seroma. **Methods:** This study comprises a two-arm randomized superiority clinical trial to evaluate the following as primary outcomes: seroma incidence, volume and duration using a suction drain and bandage safety and satisfaction as secondary outcomes. Women aged ≥18 years submitted to a mastectomy as breast cancer treatment will be included, while women submitted to bilateral mastectomies, immediate breast reconstruction or surgical flap rotation closure, who present hematomas or surgical wound infections at the time of recruitment or autoimmune diseases that lead to skin lesions and/or allergy to tape, as well as those exhibit difficulties in understanding the study will be excluded. Randomization will be performed by lots at study enrollment. Coded envelopes will be available for intervention or control group allocations. Patients allocated in the intervention group will be submitted to the bandage application for seven days. All patients will use a suction drain according to the institution's routine. **Ethics and disclosure:** This study was approved by the Brazilian National Cancer Institute, Research Ethics Committee under no. 2,774,824 and it is registered in the ClinicalTrials.gov (NCT04471142).

KEYWORDS: breast neoplasm; seroma; prevention; physiotherapy; taping.

INTRODUCTION

Seroma is the most common early complication following surgical breast cancer treatment[1,2]. Incidence rates range from 2.5% to 85%[1-3] and the condition is directly associated to extensive surgical dissection procedures, such as mastectomies and axillary lymphadenectomies, due to the generation of more dead space between tissues[4].

There are some known risk factors for the development of seroma in women undergoing surgical treatment for breast cancer, such as older age, higher body mass index (BMI), high blood pressure, large breast volume, breast biopsy prior to surgical treatment, neoadjuvant chemotherapy, thromboprophylaxis, presence of lymph node metastasis, greater number of removed lymph nodes, longer surgery times, electrocautery, type of drainage and longer suction drain durations[5-9].

Although seroma formation is not life threatening, it may comprise a risk factor for the development of necrosis and dehiscence, predisposition to sepsis, upper limb movement restriction, lymphedema and a prolonged recovery period and, consequently, delays in beginning adjuvant therapy[10,11].

The obliteration of the dead space between the tissues left by the breast and axillary content removal is discussed among approaches applied to seroma prevention, mainly by two methods, namely surgical flap fixation or external compression[3].

Neuromuscular taping and the Kinesio® Taping method have been recently introduced into the clinical practice to reduce pain and swelling, also ensuring muscle activity stability[12,13].

The purpose of neuromuscular bandage treatment during the postoperative period is to facilitate the body's natural healing process by relieving tension in the muscles involved in the

[1]National Cancer Institute, Physiotherapy Service – Rio de Janeiro (RJ), Brazil.
[2]National Cancer Institute, Clinical Epidemiology Program – Rio de Janeiro (RJ), Brazil.
***Corresponding author:** ericanfabro@gmail.com
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surgical trauma, increasing proprioception through mechanoreceptor excitation, improving blood circulation and lymphatic drainage and decreasing inflammation and pain[12,14].

Neuromuscular bandages are composed of 100% cotton fibers and heat-sensitive acrylic glue. They do not contain any chemical substances, are hypoallergenic, and their length reaches up to 140% of their original size. They must always be expanded longitudinally, and their weight and thickness are very similar to skin, both porous and resistant to water, thus allowing for gas exchanges. These bandages are manufactured with digital printing technology, so that, once applied, they present better skin adherence[13,15].

This type of bandage application in women with breast cancer has been shown to be safe and effective. Martins et al.[16], for example, evaluated the safety and tolerability of the Kinesio® Taping bandage in the control of upper limb lymphedema secondary to breast cancer, and found that no patient developed skin lesions, blisters, hyperthermia, or skin scaling and/or redness at the application site. A meta-analysis of randomized clinical trials also concluded that kinesio taping was effective and safe in the control of lymphedema secondary to breast cancer[17].

The use of neuromuscular banding for seroma treatment, although with still little scientific evidence available, may be an option for seroma prevention and treatment following breast surgery. In this regard, Bosman and Piller[18] conducted a pilot study demonstrating the use of bandaging employing the lymphatic taping technique as a non-invasive approach for seroma treatment.

Furthermore, a Phase I study, in which the safety of a compressive bandage was evaluated in patients presenting seroma secondary to surgical breast cancer treatment reported this approach as a safe method, in which only 8.8% of patients developed a skin reaction and the bandage had to be removed, while 85.7% of women felt satisfied and 68.5% reported safe use[19].

In this context, the aim of this clinical trial is to evaluate the effectiveness of a neuromuscular compressive bandaging in seroma prevention following mastectomy.

METHODS

Hypotheses

This study protocol describes a randomized clinical trial in which the application of a neuromuscular compressive bandage in women with breast cancer submitted to a mastectomy was compared to routine therapy. The hypothesis is that the use of a compressive bandage during the first postoperative week associated to a drain is effective in preventing seroma. The second hypothesis is that the compressive bandage influences the length of suction drain use, the number of aspiration punctures (when indicated), and the volume of the punctured seroma.

Study design

This is a randomized controlled clinical trial of superiority with two arms, a control group and intervention group, carried out in a single reference center for breast cancer treatment.

Patients and study site

This study was carried out in the city of Rio de Janeiro, at the Cancer Hospital III of the National Cancer Institute (HCIII/INCA), concerning women diagnosed with breast cancer submitted to mastectomy.

Eligibility criteria

Women aged 18 years or older submitted to mastectomy as surgical breast cancer treatment will be included in the study.

The exclusion criteria are: patients submitted to bilateral mastectomies as well as those submitted to immediate breast reconstruction or surgical closure with skin flap rotation, presenting hematoma or surgical wound infections at the time of recruitment, presenting autoimmune diseases that generate skin lesions and/or allergy to tape, as well as patients with difficulties in understanding the study.

Sample size

The sample size was calculated by considering the occurrence of the outcome (seroma) in 60% of the control group patients[1] and in 45% of the intervention group, at a 5% significance level and 80% test power through a one-tailed hypothesis test. This calculation indicated the inclusion of 270 patients, 135 in each group.

Randomization

Randomization will be performed by drawing lots at the moment the patient enters the study (Figure 1). A total of 27 blocks containing 10 envelopes will be made available, 5 of which will contain a code that allocates patients in group A and 5 in group B. This was established to avoid therapist or patient preferences concerning the intervention. The patients will be guided concerning their group and the follow-up will be carried out while the patient is under dressing care. All assessments, intervention and data collection will be carried out by professionals trained and qualified for this purpose.

Treatment protocols

According to the HCIII/INCA routine, a closed system used for postoperative (PO) drainage will be inserted intraoperatively in patients undergoing mastectomies or axillary dissections for seroma prevention. This system remains between seven and fourteen days, depending on the drainage volume. On the first postoperative day, all patients will be submitted to dressing at the scarring points, with the suction drain being pointed and oriented by the nursing team to clean the drain ostium only with filtered, boiled and cold water, and to apply the dressing daily,

in addition to emptying the closed drainage system and counting the drained volume twice a day.

All patients will be scheduled to return in seven days to the physiotherapy outpatient clinic for kinetic-functional, skin and healing reassessments. The drain volumes noted at home and the drain conditions will be evaluated at the nursing outpatient clinic, which assesses and cares for the dressing, in order to proceed with drain removal. The suction drain will be removed on the 7th PO day if the total volume drained on the previous day according to the patient's notes is ≤50 mL or, at the most, on the 14th PO day, regardless of the drained volume, or in the emergency cases (infection and drain externalization).

On the first postoperative day, patients may be randomized to the following groups:

- Group A (Intervention with neuromuscular banding): Patients allocated in this group will undergo neuromuscular compressive bandage on the hospital discharge day. The bandage will be removed on the 7th day, when the patient will be scheduled to return to the nursing clinic. The patients will be instructed to remove the material at home in case of any symptom such as itching, redness, discomfort and/or any other occurrence due to bandage use.
  - For bandage application:
    1. Assessment and scarring care by the nursing team.
    2. Placement of the sterile microporous tape over the scarring region to avoid contact with the bandage glue, and protect the scar points if the patient needs to remove the bandage at home. This adhesive tape is a sterile material used to protect the scarring points.
    3. Application of the 7.5 cm wide Vitaltape® neuromuscular bandage, through maximum stretching on the plastron, armpit, and lateral thorax portion regions. The bandage will be placed without stretching at both ends, using between two and three centimeters. The necessary number of bandage bundles will be applied according to the trunk height and width of each patient.

All applications will be performed by trained physiotherapists for proper neuromuscular bandage placement employing the

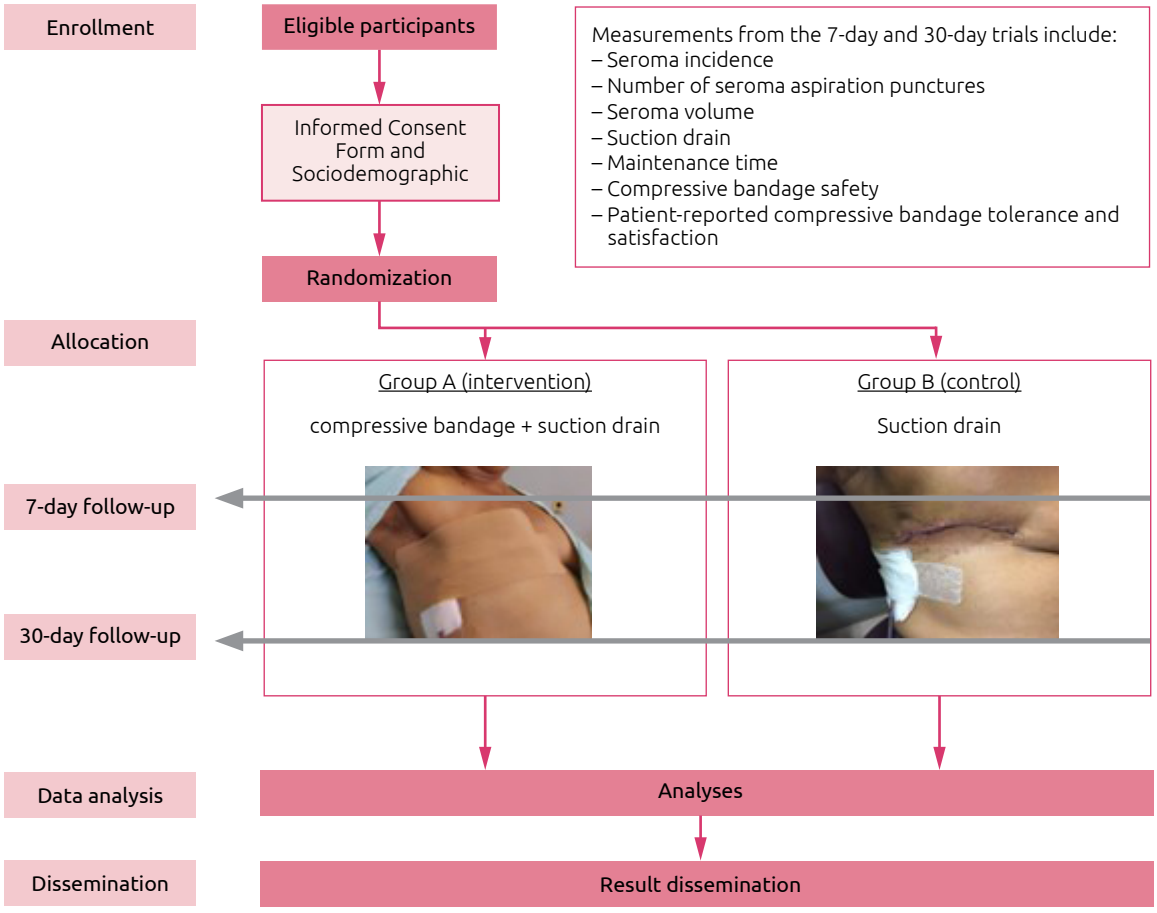

Figure 1. Study randomization protocol.

compressive technique. Research participants will receive a home guidance manual with instructions on bandage use and a home checklist that must be completed with daily observations and collected at the end of seven days (the Complementary document).

- Grupo B (control):
  The patients allocated in this group will follow the institutional routine using only the suction drain, and will be instructed by the nursing team to maintain the scarring points uncovered and wash them daily with filtered, boiled, and cold water, returning to the nursing clinic in 7 days for reassessment.

Blinding

As this survey aims to assess the use of a medical device, blinding is not possible due to the intervention characteristics. Thus, neither participants nor researchers who will assess the outcomes and collect the data will be blinded.

Data collection

Data will be collected through interviews and physical examinations, and complemented by an active search using both electronic and physical medical records. Information regarding type of oncological treatment, histopathological reports and clinical data on dressing care will be obtained from hospital records.

Patient follow-ups

Interviews and physical examinations will be performed during the study enrollment moment, and after 7 and 30 days of surgery. Data on sociodemographic characteristics and life habits will be obtained during the initial interview. After 7 days, patients in the intervention group (Group A) will be asked about local symptoms due to bandage use (concerning compressive bandage safety), as well as bandage use tolerance and satisfaction.

Outcomes parameters and statistical analysis

Primary outcome

The primary outcomes of this study will be assessed considering physical and/or electronic medical records obtained by the nursing team responsible for dressing care.

- Seroma incidence: seroma will be considered as the presence of local fluctuations with aspiration puncture indication condition for resolution, regardless of drained volume.
- Number of punctures: considered as the number of times the patient returned to the Institution to perform seroma puncture aspiration until complete resolution.
- Seroma volume: considered as the sum of all punctured volumes at each patient visit.
- Suction drain maintenance time: the time the suction drain must be maintained, in days.

Secondary outcomes

Secondary outcomes will only be evaluated in the intervention group (Group A) on the 7th postoperative day, as they are directly associated to compressive bandage use (Figure 2).

- Compressive bandage safety: any dermal alterations caused by the bandage will be evaluated.
- Compressive bandage tolerance: reports on the sensations of patient using the compressive bandage.

Descriptive and control variables

The following variables will be employed: patient characteristics (age, marital status, education, skin color, body mass index, arterial hypertension, Diabetes Mellitus status, smoking and alcohol consumption), as well as tumor characteristics, oncological treatment (clinical staging, molecular subtype, type of breast biopsy, neoadjuvant treatment (chemotherapy, targeted therapy, hormone therapy), type of breast surgery, number of removed lymph nodes, number of involved lymph nodes, use of an electric intraoperative scalpel, surgical laterality and breast weight, and postoperative complications characteristics (spontaneous dehiscence of the surgical stitches, epidermolysis, necrosis, instrumental debridement, surgical wound infection and hematoma, delayed healing, paresthesia along the course of the intercostobrachial nerve, paresthesia in the plastron, intercostobrachialgia, plastron pain, axillary net and early edema in the upper limb ipsilateral to the surgical treatment)).

Data analyses

Descriptive analysis will be performed concerning the selected variables and the main outcomes. Numerical variables will be presented using central tendency and dispersion measures, and categorical variables will be presented as frequency distributions.

The Shapiro-Wilk test will be applied to assess data distribution normality, considering a significance level of 5%. The comparison of continuous variables between the intervention groups will be performed using the Student's t test, while for categorical variables the chi-square test or Fisher's exact test will be performed. Outcome assessments for dichotomous variables will be carried out using odds ratios at a 95% confidence interval.

Multiple logistic regressions and multiple linear regressions will be performed to control confounding variables. The variables to be included in the model will be selected by the Stepwise Forward method (progressive variable inclusion), maintaining those presenting $p<0.05$

The SPSS version 24.0 will be used for the data analysis.

Ethics and dissemination

Data collection and confidentiality

Patients who meet the inclusion criteria will be informed about the purpose of the study, its duration, possible side effects and

Dermal alterations:

- Color alterations (redness): defined according to the presence of hyperemia at the bandage application site.
- Local temperature increases: defined according to the presence of hyperthemia at the bandage application site.
- Peeling: the presence of dry or wet desquamation at the bandage application site will be assessed, graded as mild, moderate or intense.
- Wounds: the presence of continuity solution (wounds) at the bandage application site will be assessed, being graded as mild, moderate or intense.
- Bullous lesions: the presence of blisters at the bandage application site will be assessed, graded as mild, moderate or intense.

Patient sensations:

- Pain at the application site: considered by patient reports and graded according to a Numerical Visual Scale (0-10).
- Pruritus: reports on itching or irritation at the bandage application site will be assessed, graded according to the Numeric Visual Scale (0-10).
- Burning: report on burning at the bandage application site will be assessed, graded according to a Numerical Visual Scale (0-10).
- Discomfort: discomfort at the application site will be assessed, graded according to a Numerical Visual Scale (0-10).
- Feeling of tightness: uncomfortable tightness will be assessed, graded according to a Numeric Visual Scale (0-10).

Figure 2. Dermal alterations and sensations referred to during the intervention period.

non-mandatory participation. Upon participation acceptance, confidentiality will be guaranteed through the confidential filing of information concerning patient health and personal data, and an informed consent form will be provided.

Patients participating in the intervention group may report discomfort at the bandage application site (itching, local heat, burning, redness, swelling, pain). Upon any complication, the intervention will be suspended. Possible discomfort monitoring and follow-up will be carried out until full patient recovery by the physiotherapy and nursing services, and by the Emergency Care Service assistance team, as this service may comprise the main gateway in case of any local discomfort due to bandage use.

Ethics

This study was approved by the National Cancer Institute Research Ethics Committee (CEP-INCA), Rio de Janeiro, Brazil, under No. 2,774,824, in accordance with attributions defined in CNS Resolution No. 466/2012 and CNS Operational Standard No. 001/2013.

This clinical trial is registered at Clinical Trials.gov under identifier No. NCT04471142.

Withdrawal

All participants are free to withdraw from the study at any time and for any reason.

Dissemination plan

This study protocol intends to answer whether the use of a compressive bandage during the first postoperative week associated with the use of a drain is effective in preventing seroma. The results of this research will be published in scientific publications, national and international scientific events, and other media portals. The study protocol will be presented to healthcare professionals and shared with patient groups through workshops and webinars.

DISCUSSION

Seroma stands out as the most common complication arising from breast cancer treatment. Its presence can increase the likelihood of developing infections, edema, and limitations in joint amplitude. This can result in setbacks for adjuvant treatment, as well as causing discomfort when engaging in daily tasks, leisure, and work.

The utilization of a compressive bandage was deemed a secure approach for patients experiencing seroma after undergoing surgical treatment for breast cancer, necessitating aspiration to alleviate discomfort.

A clinical trial was designed to explore the potential effectiveness of utilizing a compressive bandage during the initial week following mastectomy surgery, as part of the surgical treatment for breast cancer. This approach aims to offer a cost-effective strategy for preventing seroma formation.

CONCLUSIONS

The application of compressive bandage can be an effective and non-invasive strategy to prevent seroma in patients after mastectomy surgery.

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AUTHORS' CONTRIBUTIONS

EANF: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft. RMC: Data curation, Investigation, Methodology, Project administration, Writing – original draft. FOM: Investigation, Methodology, Writing – original draft. DMT: Investigation, Methodology, Writing – original draft. SSA: Formal analysis, Writing – review & editing. LCST: Supervision, Writing – review & editing. AB: Conceptualization, Data curation, Formal analysis, Supervision, Writing – review & editing.

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

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

ABSTRACT

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

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

INTRODUCTION

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

[1]Fundação Centro de Controle de Oncologia do Estado do Amazonas, Department of Mastology – Manaus (AM), Brazil.
[2]Universidade Federal do Amazonas – Manaus (AM), Brazil.
[3]Universidade do Estado do Amazonas – Manaus (AM), Brazil.
[4]Universidade Nilton Lins – Manaus (AM), Brazil.
[5]Universidade Estadual Paulista – Botucatu (SP), Brazil.
***Corresponding author:** kaiomcesar@hotmail.com
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from surgery and radiotherapy to systemic drug treatment (chemotherapy, hormone therapy)[4].

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

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

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

METHODS

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

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

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

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

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

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

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

RESULTS

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

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

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

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSIONS

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

AUTHOR'S CONTRIBUTIONS

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

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JGM: Data curation.

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Survival of patients with de novo metastatic breast cancer

Fernanda Perez Magnani Leite[1]*, Gisele Aparecida Fernandes[2], Maria Paula Curado[2], Solange Moraes Sanches[3], Livia Prôa Felippe[1], Fabiana Baroni Alves Makdissi[1]

ABSTRACT

Introduction: For the 2020-2022 trieniumm more than 2 million cases of breast cancer were estimated worldwide. De novo metastatic breast cancer is so called when metastasis is diagnosed at the same time as the primary tumor. It affects approximately 3.5 to 10% of breast cancer patients and only 25% of these will be alive after 5 years. **Methods:** We conducted a retrospective cohort study of women with de novo metastatic breast cancer treated at a single center from January 1, 2000 to December 31, 2012. Cases were identified in the Hospital Cancer Registry. Overall survival (OS) was estimated at 5 years with the Kaplan-Meier product limit, and the log-rank test was used to test differences between curves; Cox multiple regression and all tests were considered significant with p<0.05. **Results:** Of the 265 patients in the study, the estimated 5-year OS was 31.3%. There was a difference in survival according to the following: age group (p<0.046); having had breast surgery (p<0.001); having undergone chemotherapy simultaneously with radiotherapy, hormone therapy, targeted therapy or surgery (p<0.088); use of exclusive or multimodal hormone therapy (p<0.001); education (p<0.001); luminal tumors (p<0.003); and being treated between 2006 and 2012 (p=0.043). In the multiple model adjusted by age group and education, the following factors remained as predictors of a better prognosis: having undergone surgery (hazard ratio — HR=0.46, 95% confidence interval — 95%CI 0.32–0.66); luminal tumors (HR=0.34, 95%CI 0.23–0.50); and targeted therapy (HR=0.27, 95%CI 0.15–0.46). **Conclusion:** The risk of death in patients with de novo metastatic breast cancer was lower than in those undergoing local surgical treatment as part of multimodal treatment, as well as the luminal molecular subtype and the introduction of better systemic treatment strategies, such as target.

KEYWORDS: breast cancer; survival; metastasis.

INTRODUCTION

For the 2020-2022 triennium, more than 2 million cases of breast cancer were estimated worldwide, with just under 700,000 deaths, which represents a significant 15.5% of total cancer deaths in women[1,2]. In Brazil, the estimate was more than 73 thousand new cases and 18,068 deaths, with cancer being the first cause of death among women, which corresponds to 16.3% of all cancer deaths[3]. De novo metastatic breast cancer is so called when metastasis is diagnosed at the same time as the primary tumor. It affects approximately 3.5 to 10% of breast cancer patients and only 25% of these will be alive after 5 years[4-6]. It is a systemic disease that requires multimodal treatment and is classified, like the initial disease, into clinically relevant groups for treatment, according to the positivity or negativity of estrogen, progesterone and HER2 receptors[6-8]. The most frequent sites of metastases in these patients are bone, lung, liver and central nervous system[8,9]. The mutation profile is of greater complexity and heterogeneity than the initial stages[10-12]. Surgical treatment is considered in selected cases, with precise indication to control symptoms with the intention of hygienic surgery[12]. Some studies observed a positive impact on quality of life and others found an increase in overall survival (OS) when compared to patients who did not undergo surgery in the metastatic setting. A retrospective cohort analysis was conducted on the survival of de novo metastatic patients who underwent surgical treatment in relation to those who did not undergo surgery.

METHODS

This was a hospital-based retrospective cohort study with data extracted from the Hospital Cancer Registry (RHC); it

[1]A. C. Camargo Cancer Center, Breast Surgery Department – São Paulo (SP), Brazil.
[2]A. C. Camargo Cancer Center, International Research Center, Epidemiology and Statistics Nucleus – São Paulo (SP), Brazil.
[3]A. C. Camargo Cancer Center, Clinical Oncology Departament – São Paulo (SP), Brazil.
***Corresponding author:** fernanda.leite@accamargo.org.br
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was composed of women with de novo metastatic breast cancer treated in a single Brazilian center from January 1, 2000 to December 31, 2012. The sociodemographic variables analyzed were age group (≤50 years, 51–69 years and ≥70 years), education (complete and incomplete primary education, and complete secondary education and higher education), and health care (supplementary or public health care system). The molecular subtypes (luminal, HER2-positive luminal B, overexpressed HER2 and triple-negative), the histological grade (1, 2 and 3), the number of lines of chemotherapy and hormone therapy, and the topography of the metastases were analyzed. Treatment was stratified according to modality (yes and no), breast-conserving surgery (segmental resection and quadrantectomy), total mastectomy, axillary sentinel lymph node investigation, axillary dissection, chemotherapy, radiotherapy, hormone therapy and targeted therapy

The cases were staged according to the American Joint Commission of Cancer (AJCC), 8th edition, in 2018, which added histological grade, presence of estrogen/progesterone/HER2 receptors and multiple gene panel[13]. For qualitative variables, absolute (n) and relative frequency (%) were evaluated.

Survival time was calculated by subtracting the date of last information (alive or dead) by the date of diagnosis. The Kaplan-Meier product limit estimator was used to compare survival curves, and the log-rank test was applied. The semiparametric Cox proportional hazards model was used to evaluate the prognostic potential, and the hazard ratio (HR) and 95% confidence interval (95%CI) were calculated for all variables. For the multiple model, variables were selected using the log-rank test, from the highest to lowest level of statistical significance. The survival analysis was divided into two periods (2000–2005 and 2006–2012) because of the importance of the introduction of taxane drugs and targeted therapy in treating patients more effectively from 2006 onwards. The proportional hazards assumption was based on Schoenfeld residuals. The significance level for all tests was set at 0.05. All statistical analyses were performed in STATA 15 (College Station, Texas, 2017).

This study was approved by the Research Ethics Council (CEP) under No. 2660/19.

RESULTS

Between 2000 and 2012, 265 patients with de novo metastatic breast cancer were identified. Of these, 42.5% (n=90) were aged 61 or over and 78.5% (n=208) received care through the supplementary health care system. Regarding clinical staging, 51.4% (n=136) of patients were T4; 34.3% (n=91), N1; histological grade 2 was the most common, present in 47.5% (n=126) of patients (Table 1).

The molecular subtypes of the cases evaluated were: luminal (58%; n=153), HER2-positive luminal B (21%; n=56),

Table 1. Sociodemographic characteristics, clinical staging and molecular subtype of 265 patients with de novo metastatic breast cancer treated at the A. C. Camargo Cancer Center, from 2000 to 2012.

Variable	n=265	%
Age group (years)		
≤50	90	33.8
51–60	63	23.7
≥61	112	42.5
Education		
Primary, complete and incomplete	47	18.1
Secondary, complete, and Higher Education	77	28.9
Unknown	141	53.0
Health care		
Public health care system	50	18.8
Supplementary care health system	208	78.5
Not reported	7	2.6
Year of diagnosis		
2000–2005	90	33.8
2006–2012	175	66.2
T – Clinical tumor size		
Tx	4	1.5
T1	12	4.5
T2	68	25.7
T3	43	16.2
T4A/C/D	28	10.6
T4B	108	40.8
Not reported	2	0.8
N – Lymph node status		
N0	61	23.0
N1	91	34.3
N2	83	31.3
N3	28	10.5
Not reported	2	0.7
Molecular subtype		
Luminal	153	58.0
Luminal B HER2-positive	56	21.0
HER2-overexpressing	25	9.4
Triple-negative	19	7.1
No information	12	4.5
HER2*		
Negative	171	64.5
Positive	82	31.0
Not reported	12	4.3

Continue...

Table 1. Continuation.

Variable	n=265	%
Estrogen receptor		
Negative	56	21.0
Positive	202	76.0
No information	7	3.0
Progesterone receptor		
Negative	85	32.0
Positive	170	64.0
No information	10	4.0
Histological grade		
1	15	5.6
2	126	47.5
3	106	40.0
Not reported	18	6.8
Metastases (n=324)		
Bone	199	99.4
Lung	97	64.0
Liver	86	56.1
Central nervous system	40	28.5
Others	76	66.1

*HER2 + (IHC 3+ or 2+ with ISH amplified).

HER2-overexpressing (9.4%; n=25) and triple-negative (7.1 %; n=19) (Table 1).

When evaluating metastases, all patients had involvement in multiple organs, with bone being the most affected, followed by the lung and liver (Table 1).

In multimodal treatment, chemotherapy was performed in 81.9% (n=217) of patients, radiotherapy in 76.7% (n=204), hormone therapy in 66.8% (n=177); targeted therapy in 15.8% (n=42) and surgery in 32.5% (n=86) (Table 2).

The 5-year OS in patients with de novo metastatic breast cancer from 2000 to 2012 was 31.3%: 20.22% in the period of 2000 to 2005 and 34.95% in the period of 2006 to 2012. The highest survival rates were identified in women with age under 50 years (35.89%), higher education (42.2%), luminal molecular subtype (34.4%), surgical breast treatment (47.7%), axillary surgery (49.3%), radiotherapy (34.5%) and targeted therapy (54.2%) (Table 3 and Figure 1).

In the multiple regression model adjusted by age group and education, a reduction in the risk of death was observed in patients who underwent surgical treatment in the breast (HR=0.46, 95%CI 0.32–0.66), with luminal tumors (HR=0.34, 95%CI 0.23–0.50) and with HER2 tumors using targeted therapy (HR=0.27, 95%CI 0.15–0.46). An increased risk of death was also observed in patients with N2 and N3 axillary involvement (HR=1.71, 95%CI 1.12–2.62) (Table 4).

Table 2. Treatment modalities in 265 patients with de novo metastatic breast cancer at A. C. Camargo Cancer Center, from 2000 to 2012.

Treatment	n	%
Primary surgery – breast		
Yes	86	32.5
No	179	67.5
Type of breast surgery – primary		
Mastectomy (total)	71	82.5
Conservative surgery	15	17.4
Axillary surgery		
Yes	79	30.0
No	186	70.0
Type of axillary surgery		
Axillary dissection	76	96.2
Sentinal lymph node	3	3.8
Chemotherapy		
Yes	217	81.9
No	48	18.1
Hormonne therapy		
Yes	177	66.8
No	88	33.2
Targeted therapy		
Yes	42	15.8
No	223	84.2
Radiotherapy of primary lesion – breast		
Yes	68	25.6
No	244	78.2
Radiotherapy of metastases		
Yes	136	51.1
No	108	40.7
Bone	76	28.6
Central nervous system	40	15.1
Others*	20	7.4

*plastron, neuroaxis, ocular, lymph nodes.

DISCUSSION

In this study, it was possible to verify a 31.3% probability of survival of *de novo* metastatic patients within 5 years in the period from 2000 to 2012. It was observed that, among these, patients who underwent surgical treatment of the primary tumor had an increase in survival, but it was found that the most common tumor profile was luminal, which are usually tumors with a better prognosis and great possibility of drug treatment.

Table 3. Probability of survival according to sociodemographic and clinical characteristics of 265 patients with de novo metastatic breast cancer.

Variable	Death (total)	OS – 5y	p-value
Age group (years)			
≤50	68 (89)	35.89	0.046
51–69	103 (124)	28.79	
≥70	41 (51)	21.65	
Education			
Primary incomplete/complete	41 (47)	12.77	<0.001
Secondary	23 (32)	28.13	
Higher education	25 (45)	42.20	
Unknown	141		
Year of diagnosis			
2000–2005	71 (89)	20.22	0.004
2006–2012	111 (176)	34.95	
Health care			
Public health care system	41 (50)	26.18	0.897
Supplementaryl health care system	164 (208)	31.82	
Not determined	7		
Clincal staging – cT			
T0/1	9 (16)	43.75	0.016
T2	40 (68)	39.93	
T3	25 (43)	38.03	
T4 A/C/D	21 (28)	25.00	
T4B	85 (108)	20.01	
Not determined	2		
Clincal staging – cN			
N0	34 (63)	44.18	<0.001
N1	56 (91)	36.44	
N2	69 (82)	15.85	
N3	21 (27)	22.22	
Not determined	2		
Topography of metastases			
Bone	101 (152)	31.92	0.466
Lung	30 (45)	32.15	
Liver/central nervous system	51 (69)	23.92	
Luminal			
Yes	136 (212)	34.44	<0.001
No	46 (52)	11.92	
Not determined	1		
HER2			
Yes	54 (82)	33.84	0.496
No	116 (171)	30.09	
Not determined	12		
Triple-negative			
Yes	17 (19)	5.92	<0.001
No	156 (237)	32.87	
Not determined	9		
Histological grade			
1	11 (15)	25.28	0.223
2	95 (126)	35.62	
3	88 (106)	28.62	
Not determined	18		
Breast surgery			
Yes	57 (86)	47.67	<0.001
No	137 (179)	21.05	
Type of breast surgery			
Mastectomy	36 (71)	49.3	0.586
Conservative surgery	9 (15)	40.00	
Axillary surgery			
Yes	51 (79)	49.37	<0.001
No	142 (186)	21.33	
Type of axillary surgery			
Axillary dissection	38 (76)	50.00	0.801
Sentinel lymph node	2 (3)	33.33	
Chemotherapy			
Yes	173 (217)	30.77	0.088
No	35 (48)	25.89	
Radiotherapy			
Yes	124 (157)	34.53	0.008
No	101 (108)	23.12	
Targeted therapy			
Yes	26 (42)	54.19	<0.001
No	163 (223)	25.23	
Hormone therapy			
Yes	135 (177)	39.11	<0.001
No	76 (88)	11.41	
Not determined	1		
Hormone therapy lines			
0	74 (74)	10.60	<0.001
1	43 (59)	39.07	
2	43 (54)	32.67	
3	40 (56)	52.80	
Not determined	12		
Chemotherapy lines			
0	42 (44)	24.31	0.016
1	50 (69)	36.79	
2	36 (46)	30.09	
3	60 (74)	35.91	
Not determined	25		

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The significance level for all tests was set at 0.05.

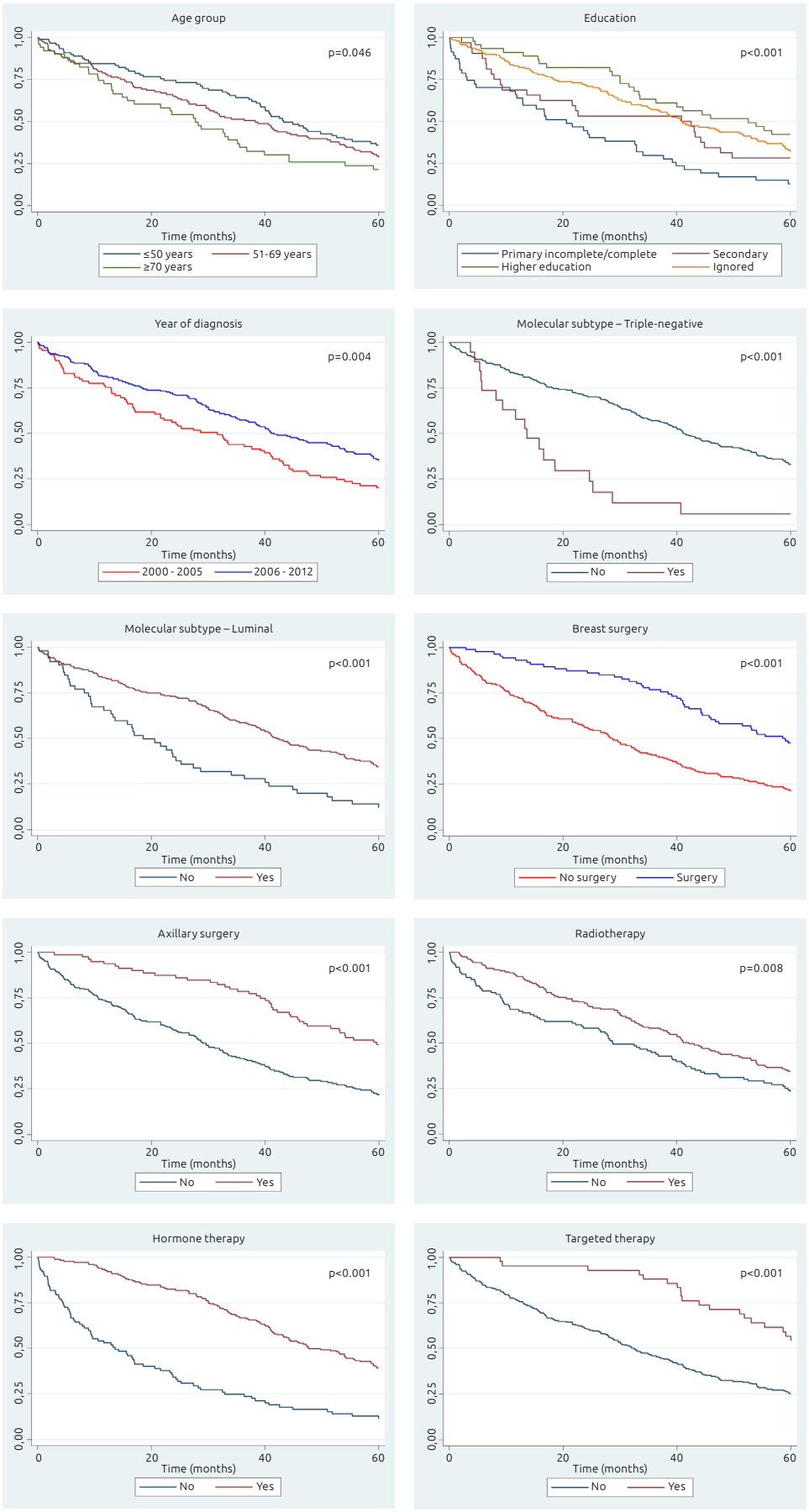

Figure 1. Estimated overall survival of 60 months for patients with de novo metastatic breast cancer.

Table 4. Prognostic factors associated with the survival of patients with metastatic breast cancer de novo at A. C. Camargo Cancer Center, from 2000 to 2012.

Variable	HR	HRa* (95%CI)
Breast surgery		
No	1.00	1.00
Yes	0.42 (0.29–0.59)	0.46 (0.32–0.66)
Luminal		
No	1.00	1.00
Yes	0.46 (0.33–0.65)	0.34 (0.23–0.50)
Targeted therapy		
No	1.00	1.00
Yes	0.38 (0.23–0.61)	0.27 (0.15–0.46)
cN		
N0	1.00	1.00
N1	1.25 (0.81–1.91)	1.21 (0.78–1.87)
N2	2.15 (1.42–3.25)	1.71 (1.12–2.62)
N3	1.80 (1.04–3.10)	1.87 (1.06–3.28)
Age group (years)		
≤50	1.00	1.00
51–69	1.25 (0.89–1.74)	0.90 (0.62–1.29)
≥70	1.67 (1.11–2.53)	0.98 (0.62–1.55)
Education		
Illiterate	1.00	1.00
Primary incomplete/ complete	0.59 (0.35–0.98)	0.72 (0.41–1.27)
Secondary	0.36 (0.22–0.60)	0.50 (0.29–0.85)
Higher education	0.48 (0.33–0.69)	0.73 (0.48–1.09)

HR: hazard ratio; 95%CI: 95% confidence interval. *Test of proportional--hazards assumption (p=0.218). Adjusted for schooling and age group.

Analyzing how these patients access care, there was no difference in survival between those treated in the public health care system and those treated in the supplementary health care system. Despite the treatment limitations imposed in the public system, access to chemotherapy and hormone therapy, at the time considered, was quite similar in our service, which was not the reality in Brazil as a whole. In the Amazona III study, a nationwide retrospective cohort that carried out an epidemiological analysis of breast cancer at all stages and evaluated the difference between patients treated by the public health care system and the supplementary health care system, it was observed that patients treated in the public system had tumors at more advanced stages and greater difficulty in accessing screening tests, which had a negative impact on their prognosis[14].

In our study, all patients were multimetastatic, with the main sites being bone, lung, liver and central nervous system, and no difference in survival was observed when evaluating the metastasis sites, which can be explained by the multiplicity of metastatic sites. In the work of Tian et al.[15], who evaluated mutations and possible biomarkers in patients with metastatic tumors and correlated them with impact on treatment and survival, liver metastases had a worse prognosis compared to other sites[15-17].

In this study, approximately 35.89% of patients were under 50 years of age, 80% belonged to the luminal subtype and regarding the combined treatment of chemotherapy, radiotherapy and surgery, 81.9% underwent chemotherapy and 32.5% surgery. This patient profile was similar to that studied in ECOG – ACRIN 2108, which evaluated surgical treatment in this group and observed no difference in OS or progression-free survival at 3 years[15]. In patients with de novo metastatic breast cancer, surgery is an option, but in the classic indication of controlling local complications, such as bleeding and infection[16]. Badwe et al.[17] found an improvement in survival in patients operated on with luminal profiles and single bone metastasis, while the ACRIN study did not observe an impact on survival[15,17].

It was observed in this study that the inclusion of surgery as part of the treatment showed an increase in survival. Our findings are consistent with those of Badwe et al.[17] and Soran et al. regarding the use of breast surgery in these patients[17,18]. It is important to note that the majority had the luminal molecular subtype, which has a better prognosis, a fact that may have influenced the results.

In clinical practice, however, the survival benefit of local treatments in de novo metastatic breast cancer is controversial. Retrospective studies have shown that local treatments increase survival, as shown in this study[17,18]. Recent randomized clinical trials[19,20] that investigated the survival benefit of primary site surgery revealed contradictory conclusions[14,15,21,22]. The reasons for this greater survival need to be studied by exploring possible mutations and genetic biomarkers, as identified in the study by Bertucci et al., from 2019, which determined the presence of mutations in nine controlling genes, such as TP53 and GATA3, among others, which impact the prognosis and survival of these patients[23]. The study concluded that metastatic disease has more mutations and greater complexity than the initial disease. Therefore, the identification of these mutations would help in conducting individualized and efficient treatment[15,23,24].

Analyzing the literature, it is possible to observe that the indication for surgery in de novo metastatic patients went through three phases: in the first, all patients underwent surgery; in the second, no patient underwent surgery; and in the third, at the moment, we individually evaluate each patient, each tumor type, disease control or progression and define cases that may benefit from surgery and those that, in fact, do not need surgery on the primary tumor[25-29].

Therefore, the study has limitations inherent to retrospective studies. However, it is a referral center specialized in cancer treatment in which data are systematically reviewed.

CONCLUSIONS

Greater survival was observed in de novo metastatic breast cancer patients whose multimodal treatment included breast surgery. However, factors such as luminal molecular subtype may have influenced these results. As the understanding of the biology of tumors evolves and treatments become more accessible to the population, our challenges will be greater in determining for whom and at what time each treatment should be carried out. What, in fact, is causing the best survival of our patients seems to us to be this quality multidisciplinary treatment.

AUTHORS' CONTRIBUTION

FPML: Investigation, Data curation, Writing – review & editing. GAF: Formal analysis, Methodology, Writing – review & editing. MPC: Formal analysis, Methodology, Writing – review & editing. SMS: Writing – review & editing, Supervision. LPF: Writing – review & editing. FBAM: Conceptualization, Project administration, Supervision, Writing – review & editing.

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ORIGINAL ARTICLE
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Assessment of the relationship between metabolic syndrome and breast cancer

Amanda Leal Guimarães[1]*, Marcelo Antonini[1], Odair Ferraro[1], Juliana Monte Real[1], André Mattar[1], Reginaldo Guedes Coelho Lopes[1]

ABSTRACT

Introduction: Metabolic syndrome (MS) affects approximately 30% of women aged over 50 years. It is known to have a direct relationship with carcinogenesis and, therefore, with breast neoplasia. **Methods:** Retrospective longitudinal observational cohort study carried out at the Gynecology and Obstetrics Service of the São Paulo State Public Servant Hospital. The rates of local recurrence, distant metastases and overall survival of patients with malignant breast neoplasia in each group were evaluated. **Results:** Between 2017 and 2020, 375 patients underwent surgical treatment for breast cancer, of which 335 were eligible for the study, with an average age of 63.4 years old. MS is present in 32.5% of patients. Regarding the prognostic factor, patients with MS have a very similar distribution. The molecular profile in patients with MS is 39.4% of Luminal A patients, while in those without MS it is 42.5% of Luminal B. Regarding clinical staging, patients with MS have initial clinical stage I and IIA in 54 .1% of cases, while patients without MS present an initial clinical stage in 65% of cases. The average overall survival of the sample was 37.3 years, with a CI of 1.1 years; disease-free survival was 35.9 years, with CI 1.2 years; and invasive disease-free survival was 36.9 years, with CI 1.3 years. **Conclusions:** The presence of MS at diagnosis does not worsen survival.

KEYWORDS: malignant breast neoplasm; metabolic syndrome; prognosis; survival.

INTRODUCTION

Metabolic syndrome (MS) can be defined as a set of conditions — central obesity (waist circumference), high blood pressure, reduced HDL cholesterol, increased triglycerides and impaired glucose intolerance — which is known to be associated with a greater risk in development of cardiovascular disease and type 2 diabetes. It affects approximately 30% of the population of women over 50 years old[1,2].

Currently, breast cancer (BC) is the most common in Brazil, after skin cancer, and is the one that causes the most deaths in the female population[3]. According to the National Cancer Institute (INCA), in 2021, around 66,280 new cases were estimated, and in 2019, more than 18,000 deaths.

The risk of developing the disease becomes higher after the age of 50, and the risk factors are numerous: behavioral (sedentary lifestyle, obesity or overweight after menopause); hormonal (early menarche, late menopause, absence of children/breastfeeding, prolonged use of oral contraceptives and hormone replacement); and hereditary (family history of ovarian or breast cancer in males, or breast cancer in women before the age of 50, in addition to genetic alterations in the BRCA1 and BRCA2 genes)[3].

In view of the aforementioned risk factors, it is important to seek, in addition to the screening recommended by the Ministry of Health (a mammogram every two years in women aged 50 to 69 years), ways to reduce the risk of BC with regard to behavioral factors. Maintaining an adequate weight and performing physical activities can contribute to reducing this pathology.

Therefore, in the pathophysiology of breast neoplasia, its relationship with MS can also be seen, which is often its cause and even its consequence. Women treated for BC seem to have an additional risk of MS, resulting from excess adiposity and the effect of treatments[4].

MS is one of the most common public health problems worldwide, and its incidence has been continuously increasing, in a pandemic manner, over the last two decades, in both developed and developing countries. Epidemiological data confirm that MS is independently associated with an increased incidence of several tumors, including BC, and is a poor prognostic factor in patients with early and metastatic BC[5].

[1]Instituto de Assistência Médica ao Servidor Público Estadual – São Paulo (SP), Brazil.
***Corresponding author:** amanda.lguimaraes@hotmail.com
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The mechanism underlying the effects of MS remains unknown. Most researchers believe that MS is related to higher concentrations of sex hormones, insulin and insulin-like growth factor, which lead to a distortion of the normal balance between cellular differentiation and apoptosis and the progression and proliferation of BC cells[6-8].

It is also noteworthy that patients with MS, with or without breast cancer, have a higher cardiovascular risk. MS is well established as a prothrombotic state associated with increased levels of inflammatory markers[1,9], which constitutes an increased risk for cardiovascular disease.

Based on this context, the present study sought to correlate prognosis in patients with malignant breast cancer undergoing surgical treatment, whether or not they had previous MS; only deaths due to BC were evaluated, and not from other causes related to metabolic complications.

METHODS

This is a retrospective longitudinal observational cohort study. Epidemiological information was collected from the database of patients in the Mastology sector of Hospital do Servidor Público Estadual (HSPE), from January 2017 to December 2020, and the patients were divided into two groups: group 1 (those who had MS) and group 2 (those who did not have these characteristics).

To define MS, the NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) criterion was based on: in order to establish the diagnosis of the syndrome, the patient must present at least three of the following five criteria: increased waist circumference (men: ≥102 cm; women: ≥88 cm); triglycerides ≥150 mg/dL; low HDL cholesterol (men <40 mg/dL; women: <50 mg/dL); high blood pressure (≥130 × 85 mmHg) and fasting blood glucose ≥100 mg/dL.

The epidemiological data obtained were many: age, date of BC diagnosis, previous comorbidities related to MS, date of recurrence or appearance of metastases, date of death due to BC, clinical staging and breakdown of the respective receptors present in each pathology.

The exclusion criteria were patients who were lost to follow-up for more than 12 months, due to an initial diagnosis of metastases, or who had missing data in the electronic medical record. All patients underwent surgical treatment at HSPE.

In both groups, the rates of local recurrence, distant metastases and overall survival of patients with malignant breast cancer were evaluated. Data were recorded in an Excel® spreadsheet and statistical analysis was conducted using the Mann-Whitney, Equality of Two Proportions and χ^2 tests.

The work was submitted to Plataforma Brasil and, as it was a retrospective study, the Free and Informed Consent Form (ICF) was waived (Figure 1).

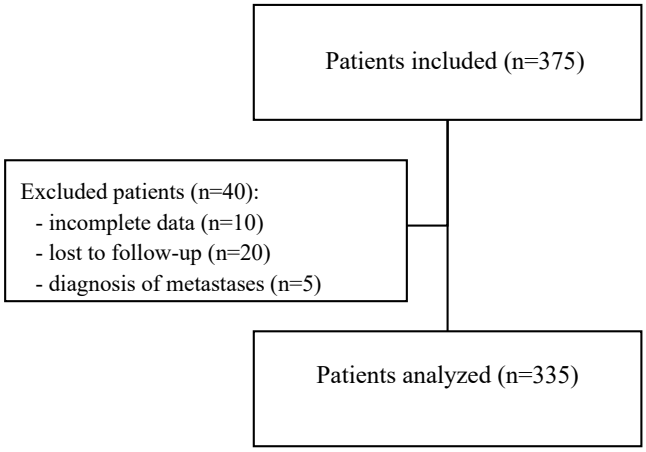

Figure 1. Patients included in the study.

RESULTS

From January 2017 to December 2020, 375 patients underwent surgical treatment for BC at HSPE, of which 25 were excluded due to loss to follow-up; 10, due to incomplete data; and five, due to diagnosis of metastases.

After exclusion, the medical records of 335 patients eligible for the study were analyzed, with mean age of 63.4±1.4 years and an average follow-up time of 48±1.4 years.

MS is present in 109 (32.5%) patients. The criteria used for MS are: waist circumference above 88 cm, HDL below 50 mg/dL, triglycerides above 150 mg/dL, diabetes mellitus or systemic arterial hypertension.

The mean age of patients with MS was 63.5±10.7 years, and of patients without MS, 65.1±10.0 years, with no significant difference. Of the patients evaluated with MS, 81.1% were menopausal, whereas of those without MS, 83.6% were menopausal. As expected, hypertension, diabetes, obesity, low HDL cholesterol, high triglycerides and waist circumference >88 cm are more recurrent among patients with MS, all with significant differences. These characteristics are shown in Table 1.

Regarding the characteristics of prognostic factors, i.e., Ki-67, molecular classification and staging, Table 2 shows that patients with MS have a very similar distribution, whereas those without MS present Ki-67 ≥14% in 62.4% of patients with a significant difference. In patients with MS, the molecular profile is 39.4% Luminal A patients, and in patients without SM, 42.5% Luminal B, with a significant difference in distribution. Regarding clinical staging, patients with MS present initial clinical stage I and IIA in 54.1% of the cases, advanced stage IIB in 20.2% and III in 25.7%, whereas patients without MS present initial clinical stage in 65% of cases, advanced stage IIB in 11.1% and III in 23.9%, results with a significant difference. When we evaluated the presence of obesity as a factor that worsens prognostic factors, we did not find significant differences. Table 2 shows these characteristics.

Table 1. Comparison of groups with and without metabolic syndrome.

	With MS (n=109)		Without MS (n=226)		p-value
Age (mean ± standard deviation) – years	63.5±10.7		65.1±10.0		0.85
BMI (mean ± standard deviation)	28.2±4.1		27.9±4.0		0.85
	n	%	n	%	
Menopausal *status*					
Pre-menopause	20	18.4	37	16.4	<0.001
Post-menopause	89	81.6	189	83.6	
Low HDL cholesterol (<50)	37	33.9	9	3.4	<0.001
Waist circumference >88 cm	49	44.9	42	18.6	<0.001
High triglycerides (>150)	82	75.2	13	5.7	<0.001
DM	81	74.3	21	9.3	<0.001
SAH	101	92.2	78	34.5	<0.001
Obesity	59	54.1	41	18.1	<0.001

MS: metabolic syndrome; BMI: body mass index; DM: diabetes mellitus; SAH: systemic arterial hypertension.
Source: database of the Mammary Pathology sector of Hospital do Servidor Público Estadual.

In the assessment of recurrences, diagnosis of metastases and deaths, there was a significant difference between the groups of patients with and without MS — relapses occurred in 4.6% of patients with MS and in 4.0% of patients without MS; metastases, in 8.3% of patients with MS and in 10.2% of patients without MS; and deaths, at 4.5% and 4.0%, respectively. When we re-evaluated obesity as a factor in worsening of recurrences, metastases and deaths, we found no differences, as can be seen in Table 3.

To evaluate the relationship between MS and adverse prognosis, a factor called "Prognosis" was created, which is the joint analysis of information on metastasis, recurrence and death. If the person presents at least one of these three factors, the prognosis is not considered a Good Prognosis, that is, only those who do not present these three factors will have a Good Prognosis. Therefore, a multivariate Logistic Regression analysis was carried out to determine the probability of a person having a Bad Prognosis based on the results of two independent factors: Ki-67 and Immune. This multivariate analysis was carried out for each MS group, that is, there are two statistical models, as shown in Table 4.

Since the two independent factors are qualitative, one of their classifications is the reference response. Thus, in KI-67, the reference is the classification of <14%, and in molecular profile, it was the best of them, that is, LUMINAL A.

Analyzing both models, it can be seen that only the TNBC classification proved to be statistically significant in the multivariate analysis — the coefficient was positive and, consequently, the odds ratio (OR) was greater than 1.00. In the non-MS model, the OR of triple negative tumors (TNBC) was 9.30, which shows that a patient with a TNBC molecular profile is 9.30 times more likely to have a poor prognosis than a LUMINAL A patient.

The temporal outcomes of overall survival, disease-free survival and invasive disease-free survival were assessed. The average overall survival of the sample was 37.3 years, with CI of 1.1 years; disease-free survival was 35.9 years, with CI of 1.2 years; and invasive disease-free survival was 36.9 years, with CI of 1.3 years. When these outcomes were compared with the presence of MS, a significant difference was observed in all outcomes.

DISCUSSION

Metabolic syndrome (MS), also known as insulin resistance syndrome or syndrome X, is a type of multifactorial metabolic disease[9]. Pathologically, patients with MS are characterized by chronic inflammation and oxidative stress, both involved in the process of carcinogenesis[10]. In the study in question, MS was present in 109 (32.5%) patients, while 226 (67.5%) were not carriers.

A literature review by Li et al., from March 2021[11], evaluates that MS and its components exert a great influence on the breast tumor and its microenvironment. In obese individuals — represented, in the present study, by 54% of patients with MS and 18% of patients without MS —, this tumor microenvironment presents a higher production of fibroblasts, immune and endothelial cells.

In the mammary gland, the interaction between obese adipocytes and BC cells leads to the transformation of mammary adipocytes into cancer-associated adipocytes, the so-called CAAs, which secrete more leptin and reduce adiponectin production[9]. These alterations show a close relationship between obesity and more aggressive BC phenotypes — increased size, high-grade tumors, triple negative tumors or tumors with multiple metastases[12].

Table 2. Distribution of prognostic factors (Ki-67, molecular profile and clinical staging) and the relationship with metabolic syndrome.

	With MS		Without MS		Total		p-value
	n	%	n	%	n	%	
General							
TNBC	23	21.1	26	11.5	49	14.6	0.010
HER-2 +	6	5.5	12	5.3	18	5.4	
Luminal HER	7	6.4	26	11.5	33	9.9	
Luminal B	30	27.5	96	42.5	126	37.6	
Luminal A	43	39.4	66	29,2	109	32.5	
Not obese							
TNBC	12	24.0	20	10.8	32	13.6	0.030
HER-2 +	3	6.0	8	4.3	11	4.7	
LUminal HER	4	8.0	22	11.9	26	11.1	
Luminal B	12	24.0	81	43.8	93	39.6	
Luminal A	19	38.0	54	29.2	73	31.1	
Obese							
TNBC	11	18.6	6	14.6	17	17.0	0.578
HER-2 +	3	5.1	4	9.8	7	7.0	
Luminal HER	3	5.1	4	9.8	7	7.0	
Luminal B	18	30.5	15	36.6	33	33.0	
Luminal A	24	40.7	12	29.3	36	36.0	
General (%)							
<14	54	49.5	85	37.6	139	41.5	0.038
≥14	55	50.5	141	62.4	196	58.5	
Not obese (%)							
<14	24	48.0	70	37.8	94	40.0	0.193
≥14	26	52.0	115	62.2	141	60.0	
Obese (%)							
<14	30	50.8	15	36.6	45	45.0	0.159
≥14	29	49.2	26	63.4	55	55.0	
General							
I	24	22.0	83	36.7	107	31.9	0.041
IIA	35	32.1	64	28.3	99	29.6	
IIB	22	20.2	25	11.1	47	14.0	
IIIA	13	11.9	30	13.3	43	12.8	
IIIB	9	8.3	19	8.4	28	8.4	
IIIB I	2	1.8	3	1.3	5	1.5	
IIIC	4	3.7	2	0.9	6	1.8	
Not obese							
I	14	28.0	69	37.3	83	35.3	0.212
IIA	15	30.0	50	27.0	65	27.7	
IIB	10	20.0	21	11.4	31	13.2	
IIIA	4	8.0	24	13.0	28	11.9	
IIIB	5	10.0	18	9.7	23	9.8	
IIIB I	0	0.0	2	1.1	2	0.9	
IIIC	2	4.0	1	0.5	3	1.3	
Obese							
I	10	16.9	14	34.1	24	24.0	0.453
IIA	20	33.9	14	34.1	34	34.0	
IIB	12	20.3	4	9.8	16	16.0	
IIIA	9	15.3	6	14.6	15	15.0	
IIIB	4	6.8	1	2.4	5	5.0	
IIIB I	2	3.4	1	2.4	3	3.0	
IIIC	2	3.4	1	2.4	3	3.0	

MS: metabolic syndrome; TNBC: triple negative tumors.
Source: database of the Mammary Pathology sector of Hospital do Servidor Público Federal.

Table 3. Comparison of metabolic syndrome with the presence or absence of metastasis.

	With SM		Without SM		Total		p-value
	n	%	n	%	n	%	
Metastases							
General							
No	100	91.7	203	89.8	303	90.4	0.575
Yes	9	8.3	23	10.2	32	9.6	
Not obese							
No	46	92.0	163	88.1	209	88.9	0.436
Yes	4	8.0	22	11.9	26	11.1	
Obese							
No	54	91.5	40	97.6	94	94.0	0.211
Yes	5	8.5	1	2.4	6	6.0	
Relapses							
General							
No	104	95.	217	96.0	321	95.8	0.795
Yes	5	4.6	9	4.0	14	4.2	
Not obese							
No	48	96.0	177	95.7	225	95.7	0.920
Yes	2	4.0	8	4.3	10	4.3	
Obese							
No	56	94.9	40	97.6	96	96.0	0.507
Yes	3	5.1	1	2.4	4	4.0	
Deaths							
General							
No	91	83.4	206	91.1	297	88.6	?
Yes	18	16.6	20	8.9	38	11.4	
Not obese							
No	40	80	167	90.0	207	88.1	?
Yes	10	20	18	10.0	28	11.9	
Obese							
No	51	86.5	39	95.1	90	90	?
Yes	8	13.5	2	4.9	10	10	

MS: metabolic syndrome.
Source: database of the Mammary Pathology Sector of Hospital do Servidor Público Federal.

Another factor that explains the association of MS with carcinogenesis is the increase in plasma estrogen concentrations resulting from the aromatization of peripheral androgens in adipose tissue. The synthesis of estrogens is catalyzed by the aromatase enzyme, which is expressed in increased amounts in the adipose tissue of the mammary gland, abdomen, hips and muscles[12]. Continuous exposure to this hormone, caused by obesity, therefore favors mitotic activity at the aforementioned sites.

In the present study, diabetes mellitus (DM) was the most frequent component of MS, second only to arterial hypertension. The hyperinsulinemia found in diabetic patients also has a clear relationship with increased body mass index (BMI). Chronic exposure to the hyperinsulinemic state stimulates DNA synthesis and, therefore, epithelial cell replication[12].

In general, the inflammatory profile of MS patients is a result of the fact that adipose tissue contains a large source of inflammatory cytokines (TNF-alpha, IL-1y and IL-6). These substances promote and generate greater insulin resistance and, therefore, the overproduction of insulin and IGF-1, with direct effects on tumor genesis[12].

This study evaluated 335 eligible patients, with mean age of 63.4±1.4 years and an average follow-up time of 48.0±1.4 years. Interestingly, in these patients, the majority of whom were postmenopausal, the presence of MS at diagnosis did not worsen

Table 4. Logistic Regression Model for worse prognosis.

	Coef. (B)	p-value	Odds ratio		
			OR	Lim. inferior	Lim. superior
With MS					
Constant	-2.277	<0.001			
KI-67 (≥14%)	-0.286	0.700	0.75	0.18	3.21
Luminal B	1.353	0.161	3.87	0.58	25.67
Luminal HER	1.604	0.170	4.97	0.50	49.24
HER-2 +	1.724	0.109	5.61	0.68	46.02
TNBC	1.871	0.036	6.49	1.13	37.20
Without MS					
Constant	-1.981	<0.001			
KI-67 (≥14%)	-0.818	0.153	0.44	0.14	1.36
Luminal B	1.027	0.135	2.79	0.73	10.72
Luminal HER	0.827	0.272	2.29	0.52	10.02
HER-2 +	1.621	0.079	5.06	0.83	30.91
TNBC	2.231	0,003	9.30	2.15	40.36

OR: odds ratio; MS: metabolic syndrome.
Source: database of the Mammary Pathology Sector of Hospital do Servidor Público Federal.

overall survival, disease-free survival or invasive disease-free survival. Despite going against what the literature shows, there are published studies that still question the real veracity of the relationship we seek to explain.

The first meta-analyses cited in the literature in 2013 and 2014 showed that MS may be a risk factor for BC, particularly in postmenopausal patients[10,13,14]. This conclusion was reached because the small number of studies included — only nine observational studies were available at the time — did not allow for in-depth analysis of factors such as menopausal status, ethnic groups, and histopathological characteristics of the tumor[10].

To try to evaluate this information, Guo et al., in November 2019[10], carried out a new updated meta-analysis seeking to better correlate MS and breast cancer. The analyses showed that MS was associated with an increased risk of BC in postmenopausal women, but this risk was reduced in premenopausal women. The 19 datasets, with 17 studies each, supported the idea that the menopausal status of patients may modify the association between MS and the incidence of BC, even under potentially unclear reasons.

When we look at TNBC, the impact of MS remains controversial. In May 2021, Yuan et al. designed a study to specifically examine mortality after diagnosis of TNBC by metabolic risk components in 544 postmenopausal women participating in the Women's Health Initiative (WHI)[15-17].

The conclusion was a 27% lower overall survival in patients with metabolic components associated with TNBC. However, in this study, patients who had MS coincidentally had lower income, were black and had lower attendance in follow-up exams, which may have indirectly contributed to the result.

In 2020, Buono et al., in a prospective observational study, observed that MS was significantly associated with an increased risk of overall death and death from BC in patients with early BC receiving neoadjuvant therapy at a median follow-up time of 7.1 years[17,18]. Although the results are inconsistent with the present study, it is noteworthy that, in the 2020 study, the lack of information on treatments for hypertension, dyslipidemia and diabetes may have underestimated the number of patients with BC.

Among the possible and main limitations of the present study are the small number of patients included, which led to divergence of results in relation to what is reported in the literature, and the effective treatment of MS, with compensation for associated factors (dyslipidemia, obesity, hyperinsulinemia and hypertension), which corroborates with lower tissue inflammatory and proliferative exposure of cancer cells.

It is important to remember that this study did not evaluate deaths from other causes, only from BC — the increased cardiovascular risk present in MS and its complications were not included in the statistics.

In view of these limitations, it is necessary to increase the number of medical records analyzed, as well as in-depth research, through recent laboratory tests, in order to assess the degree of real metabolic decompensation of patients with MS and breast cancer.

CONCLUSIONS

In this study, the presence of MS at the diagnosis of BC does not worsen overall survival, disease-free survival and invasive disease-free survival.

In multivariate analysis, triple-negative tumors — with or without MS — had a worse prognosis.

AUTHORS'CONTRIBUTION

ALG: Methodology, Writing – original draft. MA: Conceptualization, Data curation, Methodology, Writing – review & editing. OF: Validation, Visualization. JMR: Supervision. AM: Supervision. RGCL: Supervision.

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ORIGINAL ARTICLE
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Impact of the COVID-19 pandemic on breast surgery in a reference service for breast cancer treatment

Luiza Herdy Boechat Luz Tiago[1], Carolina Dalla Santa Dal Moro[1], Carolina Odorizzi Magno Nunes[1], Fernando Vivian[1], Karine Santos de Azevedo[1], Marília Damo[1], Marjoriê Aparecida Dalla Lana[1], Thaís Hunoff Ribeiro[1]*

ABSTRACT

Introduction: The pandemic caused by the spread of the SARS-CoV-2 virus posed unprecedented challenges to health systems and societies worldwide. Among the greatest challenges was the importance of balancing the treatment of patients with potentially lethal diseases alongside the pandemic. Treatment for breast cancer, a time-dependent disease, was also compromised, as financial resources, supplies, medicines, and, especially, hospital beds needed to be allocated to assist those infected with the new coronavirus. Surgeries were suspended and surgical centers closed. To compare the number of breast surgical procedures before and during the pandemic and assess their impact on the proportional number of surgeries performed. **Methods:** This is a retrospective cohort study, reviewing procedures recorded from January 2015 to June 2021. **Results:** A total of 899 patients were included, the majority of whom were female; 58.5% of cases were oncological. The most prevalent surgery in both periods was conservative oncology (sectorectomy or quadrantectomy). There was a significant difference in the number of procedures performed before and during the COVID-19 outbreak, with a 43% drop during the pandemic. There was no significant difference in the pattern of surgeries. **Conclusion:** The pandemic caused a significant reduction in the total number of elective surgical interventions in the period analyzed — a delay that the literature identifies as a potential risk factor for disease progression and increased death rates.

KEYWORDS: pandemics; breast neoplasms; covid-19; elective surgical procedures.

INTRODUCTION

The first cases of severe acute respiratory syndrome 2 (SARS-CoV-2), caused by coronavirus 2019 (COVID-19), were documented in December 2019 and rapidly disseminated worldwide[1]. In Brazil, the first confirmed case was identified on February 26, 2020, at Albert Einstein Hospital, in São Paulo. The World Health Organization (WHO) officially declared the pandemic on March 11th, 2020[1,2]. The unexpected surge in demand for treating COVID-19 patients, coupled with the need to establish and sustain the treatment of other pathologies like cancer, exerted substantial pressure on healthcare services and instigated societal transformations[3].

According to data from the Brazilian Society of Cancerology (*Sociedade Brasileira de Cancerologia* — SBC), cancer stands as one of the major global public health problems and the second leading cause of deaths (accounting for one in every six deaths) in the world[4].

In Brazil, 625 thousand new records of the disease were projected for each year of the 2020–2022 triennium. Non-melanoma skin cancer emerged as the most prevalent, followed by breast and prostate cancer in females and males, respectively[5].

One of the preventive and control measures implemented by public authorities during the COVID-19 pandemic was the provisional suspension of elective surgical procedures[4]. These measures aimed to redirect resources to address the pandemic, by preserving hospital beds for patients with respiratory infections, particularly in intensive care units[4,6]. The debate surrounding the postponement of cancer treatment is controversial, since the definition of severity depends on the type of cancer and staging[7].

Data from the National Cancer Institute (*Instituto Nacional de Câncer* – INCA) estimated an incidence of 66,280 new cases of breast cancer in women in 2020, a disease responsible for around 18,000 deaths in 2019[8].

[1]Universidade de Caxias do Sul – Caxias do Sul (RS) Brazil.
***Corresponding author:** thaishribeiro@gmail.com
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As reported by the Brazilian Society of Oncological Surgery (*Sociedade Brasileira de Cirurgia Oncológica* – SBCO), in April and May 2020, the number of cancer-related surgeries decreased by 70%, and biopsies were reduced by 50 to 90%. It is estimated that between 50 and 90 thousand Brazilians were deprived of a cancer diagnosis in the first two months of the pandemic[4].

In major Brazilian hospitals like Albert Einstein, in São Paulo, the decline in the volume of oncological surgeries, from March to May 2020, amounted to a 60% reduction compared to the corresponding period in 20192. At Hospital A.C. Camargo Cancer Center, also in São Paulo, the number of patients undergoing breast surgery during the same three months of 2020 was 13.17% lower than the figures recorded in the same quarter of 2019[9].

In the United States and Europe, the decrease in cancer patient visits per week during the pandemic's peak infection rate was 44%[9]. In England, postponing cancer surgeries for six months is projected to elevate the mortality rate of cancer patients by 30% over five years, regardless of age, site, and stage of the disease[10]. In the United Kingdom, a 20% rise in mortality from cancer, including breast cancer, is expected as a result of the pandemic[11].

Caxias do Sul, the second most populous city in Rio Grande do Sul, experienced its most challenging period of the pandemic between March and July 2021, according to data from the State Health Secretariat (*Secretaria Estadual de Saúde* – SES). The department recommended the cancellation of elective surgeries for 30 days on February 22nd and again on May 25th of that year[12].

Delays in medical care, diagnosis, and initiation of treatment are strongly associated with a worsening of the prognosis of patients with breast cancer, potentially impacting survival rates[3]. Evaluating the risks and benefits of therapeutic and diagnostic measures requires personalized consideration, taking into account the oncological prognosis and the risk of COVID-19 transmission, especially in regions with high transmissibility[1,3].

Thus, the primary aim of this research was to compare the number of surgical procedures performed by the mastology team at Hospital Geral de Caxias do Sul in the pre-pandemic period, from January 2015 to February 2020, in relation to the pandemic phase, from March 2020 to June 2021. Additionally, the study endeavors to ascertain the proportion of procedures performed during both periods and to compare the pattern of interventions over the years.

METHODS

Type of study

This is a retrospective cohort study.

Population and sampling

The group studied consists of a review of 905 cases involving patients who underwent surgical procedures carried out by the mastology team, from January 2015 to June 2021, at Hospital Geral de Caxias do Sul, a regional reference health facility in oncology for patients in the mountainous region of Rio Grande do Sul, Brazil.

Inclusion and exclusion criteria

The study included 899 patients who underwent surgery by the mastology team, at Hospital Geral de Caxias do Sul, from January 2015 to June 2021, regardless of gender and the purpose of the surgery — whether therapeutic, diagnostic, reconstructive, or aesthetic. Six cases were excluded from the study due to incomplete surgical information found in the electronic medical records.

Data collection

The data were extracted from the electronic medical records of the operated patients through a comprehensive review of the surgical maps for the period studied. These data were then tabulated in an Excel® spreadsheet, whose access was restricted to research participants, respecting the confidentiality agreement.

Analysis and interpretation of data

The information collected was analyzed from the database created. The significance level adopted was 0.1% ($p<0.001$).

The qualitative variables were analyzed by calculating their absolute and relative frequencies and the quantitative variables, using standard deviation and central tendency (mean, mode, or median). To compare patients, χ^2 was used, based on two models. The analysis focused on comparing the number of surgical procedures conducted during the pre-pandemic years with those performed during the COVID-19 outbreak.

Ethical aspects

The researchers involved committed to keeping the data confidential, in accordance with the confidentiality agreement. The work was submitted to the Plataforma Brasil ethics committee. The study was approved by the Scientific and Editorial Board (*Conselho Científico e Editorial* – COEDI) of Fundação Universidade de Caxias do Sul — Hospital Geral.

RESULTS

Population analysis

899 patients who underwent surgery between January 2015 and June 2021 were included in the study, 868 of whom were female (96.6%). Of the total cases, 58.5% referred to cancer patients. Due to the diversity in surgical names and to standardize the analysis, patients were classified into seven surgery categories:

1. Conservative: sectorectomies and quadrantectomies in patients without a diagnosis of malignant neoplasia, such as resection of fibroadenomas, intraductal papillomas, ductal

ectasia, any benign tumors, recurrent abscesses, and other benign pathologies;
2. Oncological conservative: sectorectomies or quadrantectomies with an axillary approach, as indicated, in patients diagnosed with malignant neoplasia;
3. Mastectomy: complete removal of the mammary gland, with or without preservation of the nipple-areolar complex and the skin;
4. Mastectomy + reconstruction: complete removal of the mammary gland, with or without preservation of the nipple-areola complex and skin, and invariably includes reconstruction with an expander or silicone prosthesis;
5. Aesthetic, reparative, or corrective: excision of accessory mammary glands, resection of supernumerary nipples, prosthetic implants to repair congenital defects and genetic anomalies, mastopexies, reduction mammoplasties, and correction of gynecomastia;
6. Lymphadenectomy: excision of lymph nodes for diagnostic and/or therapeutic purposes;
7. Reconstruction: implantation of a silicone prosthesis or expander following oncological surgery.

Grouped by type of procedure, the analysis revealed that 315 patients underwent breast-conserving oncological surgery, constituting 35% of the sample and representing the most prevalent surgical indication. Another 263 cases involved non-oncological conservative surgery, accounting for 29.3% of the total. Mastectomy was performed in 109 cases (12.1%), while 101 cases involved aesthetic, reparative, or corrective surgery (11.2%). Additionally, 80 cases (8.9%) involved mastectomy with reconstruction, 20 cases (2.2%) were categorized as reconstruction procedures, and 11 cases (1.2%) involved lymphadenectomies (Table 1).

When comparing periods, the number of surgeries performed each year was as follows: 124 surgeries in 2015 and, successively, 139 in 2016; 146 in 2017; 160 in 2018; 173 in 2019; 123 in 2020, and 34 in the first half of 2021 (Table 2).

It is possible to observe the number of procedures in each semester of the period in Graphic 1.

Table 1. Surgical procedures performed from January 2015 to June 2021.

By type of surgery	Quantity (%)
Conservative	263 (29.3)
Oncological conservative	315 (35.0)
Mastectomy	109 (12.1)
Mastectomy + reconstruction	80 (8.9)
Cosmetic, reparative, or corrective	101 (11.2)
Lymphadenectomy	11 (1.2)
Reconstruction	20 (2.2)
Total	899 (100)

Pre-pandemic period

From January 2015 to February 2020, a total of 774 surgical procedures were recorded. Of this total, 57.1% were due to malignant breast neoplasia. Oncological conservative surgeries were also the most prevalent, accounting for 260 procedures (33.6%), followed by 232 non-oncological conservative surgeries (30%), 97 cosmetic, reparative, or corrective surgeries (12.5%), 95 mastectomies (12.3%), 65 mastectomies with immediate reconstruction (8.4%), 18 reconstructions (2.3%), and 7 lymphadenectomies (0.9%) (Table 3).

For direct comparison over the same number of months, in the 16 months immediately prior to the pandemic, from December 2018 to February 2020, a total of 220 procedures were recorded.

Pandemic period

Since the onset of the pandemic in March 2020 until the end of the first half of 2021 (16 months), a total of 125 surgeries were performed. Among these, 91 surgeries occurred between March and December 2020, and 34 in the first half of 2021. Notably, 67.2% of these patients were diagnosed with breast cancer.

Oncological conservative surgery remained the most frequent procedure, totaling 44% of cases, followed by 31 non-oncological conservative surgeries (24.8%), 15 mastectomies with immediate reconstruction (12%), 14 mastectomies (11.2%), 4 cosmetic, reparative, or corrective surgeries (3.2%), 4 lymphadenectomies (3.2%), and 2 reconstructions (1.6%) (Table 3).

It is possible to compare the proportion of procedures in the two periods in Graphic 2.

The χ^2 test was used to analyze the number of surgeries before and during the pandemic. There was a statistically significant difference, indicating a reduction in the number of procedures during the pandemic. The likelihood ratio was 20.58 and Pearson's χ^2 was 19.21.

DISCUSSION

The data from this research substantiated the hypothesis of a disparity between the number of surgical procedures prior to the pandemic and during the COVID-19 outbreak, wherein a 43% reduction was observed, consistent with findings from similar studies[2,9].

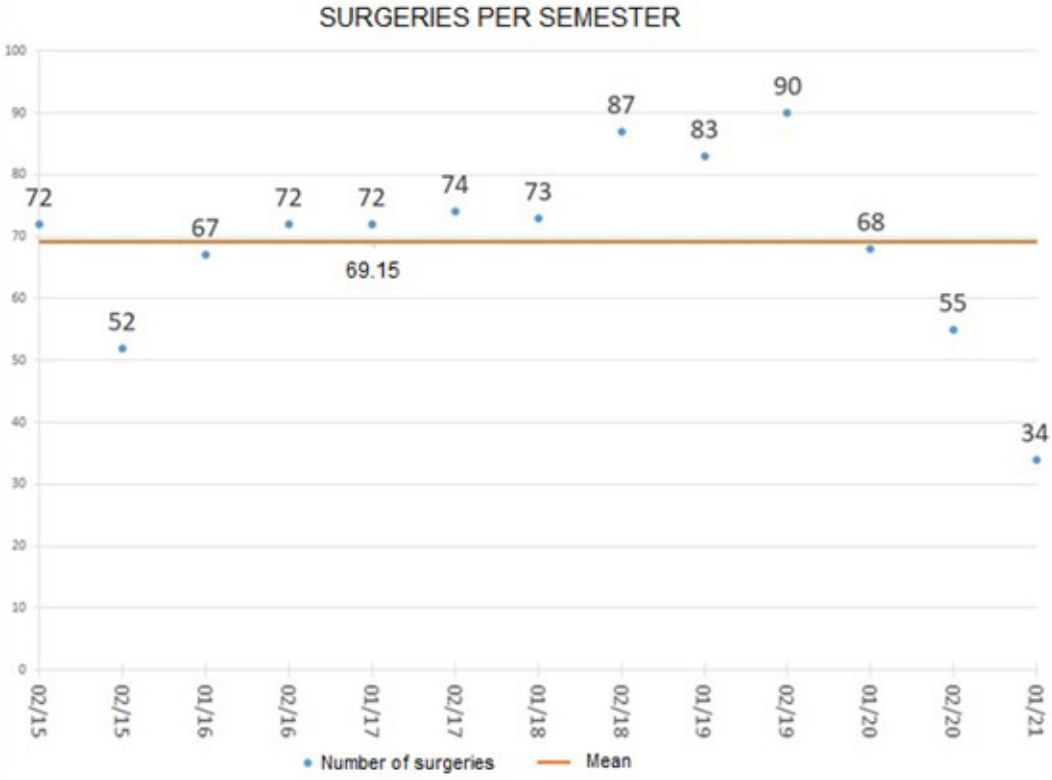
It is evident that conservative surgeries remained the most performed, especially oncological surgeries, regardless of the period evaluated. This fact reflects an evolution in increasingly earlier diagnosis, combined with advances in cancer treatment, such as neoadjuvant treatment. Furthermore, the multidisciplinary approach to patient care enables the implementation of less invasive surgical techniques.

The study also revealed a progressive increase in the total number of surgeries over the years, a phenomenon driven by population growth and the positioning of the service as a regional reference.

Table 2. Surgical procedures performed annually.

Surgery	2015	2016	2017	2018	2019	2020	2021*
Conservative	46	43	48	46	46	26	8
Oncological conservative	23	40	50	62	73	47	20
Mastectomy	22	13	14	22	20	16	2
Mastectomy + reconstruction	8	14	14	10	17	14	2
Cosmetic, reparative, or corrective	23	23	16	12	12	15	0
Lymphadenectomy	2	4	0	1	0	3	1
Reconstruction	0	1	4	7	5	2	1
Total	124	139	146	160	173	123	34

*First Half of 2021.



Graphic 1. Frequency of surgeries per semester in the period.

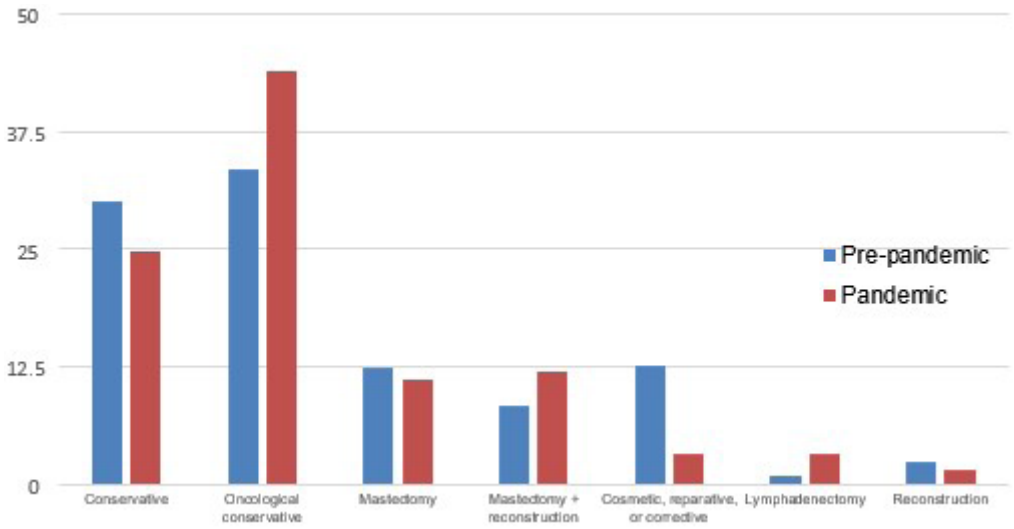
Table 3. Number of procedures performed in the pre-pandemic and pandemic periods.

Surgery	Pre-pandemic (%)	Pandemic (%)
Conservative	232 (30.0)	31 (24.8)
Oncological conservative	260 (33.6)	55 (44.0)
Mastectomy	95 (12.3)	14 (11.2)
Mastectomy + reconstruction	65 (8.4)	15 (12.0)
Cosmetic, reparative, or corrective	97 (12.5)	4 (3.2)
Lymphadenectomy	7 (0.9)	4 (3.2)
Reconstruction	18 (2.3)	2 (1.6)
Total	774 (100)	125 (100)

In 2015, 124 surgeries were registered, which increased to 139 in 2016 (12%), 146 in 2017 (5%), 160 in 2018 (9%), and 173 in 2019 (8%).

With the onset of the pandemic, there was a 28% reduction in the number of procedures in 2020 (123) compared to 2019; in the first half of 2021, the lowest volume of surgeries was recorded within the period analyzed, applying proportionality.

Comparing the 16 months immediately prior to the pandemic with the 16 months analyzed during the pandemic, the decline in the number of procedures reached 43%. This reduction corresponds to the phase marked by the most significant restrictions on scheduling elective procedures, coinciding with the peak of the pandemic in Caxias do Sul, experienced in the first half of 2021. The impact of COVID-19 on surgery schedules underscores the harm inflicted upon breast cancer patients during this period.



Graphic 2. Frequency of surgeries by period.

Despite the dedication of the administration and all healthcare teams to uphold care for cancer patients, the surgical schedule endured sacrifices and many procedures were suspended during the most critical periods witnessed so far. The long-term repercussions of these delays, added to delays in the diagnosis of breast cancer, will have consequences that can be quantified in new studies.

CONCLUSIONS

The outcomes of this research converged with other studies that also demonstrated a significant reduction in the volume of surgeries during the pandemic period compared to the pre-pandemic period. There is potential for the study to progress by comparing larger samples, as the spread of COVID-19 has not yet come to an end. Furthermore, in the long term, it may be valuable to observe whether there is any discernible impact on the survival rates of our patients.

AUTHORS' CONTRIBUTION

LHBLT: Conceptualization, Formal analysis, Investigation, Project administration, Methodology, Supervision, Validation, Writing – review & editing. CDSDM: Data curation, Software, Visualization. COMN: Data curation, Software, Visualization. FV: Conceptualization, Formal analysis, Investigation, Project administration, Methodology, Supervision, Validation, Writing – review & editing. KSDA: Data curation, Software, Visualization. MD: Data curation, Software, Visualization. MADL: Data curation, Software, Visualization. THR: Data curation, Software, Visualization.

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In vivo localization of occult lesions and margins in breast carcinoma using radio-fluorescence: a new hybrid technique

Antônio César Pereira[1]*, Sonia Marta Moriguchi[2], Mara Costa Dutra[3], Rogério Bizinoto Ferreira[4], Alexandre Marchiori Xavier de Jesus[5], Délio Marques Conde[6], Sebastião Alves Pinto[7], Jorge Rodolfo Beingolea[8]

ABSTRACT

Objective: The aim of this study was to present a new technique for hybrid marking of non-palpable breast lesions and *in vivo* evaluation of surgical margins, called Fluorescence and Seed for Hybrid Intraoperative Evaluation. **Methods:** Seven women with non-palpable breast lesions and suspected or confirmed malignancy underwent prior iodine-125 seed implantation and peripheral intravenous administration of indocyanine green 30 min before surgery. A hybrid gamma probe with an optonuclear probe was used to detect gamma radiation in the lesions and, sequentially, the fluorescence mode, in the same lesion and its margins, after its removal. **Results:** This method distinguished, in real time, one benign and six malignant lesions, guiding the removal, identifying the remaining neoplastic area in the surgical bed, and allowing its intraoperative enlargement. **Conclusion:** This pilot study evaluates the feasibility of this new technique in identifying the primary lesion and controlling surgical margins using hybrid technology.

KEYWORDS: breast cancer; surgical margins; indocyanine green, nuclear medicine.

INTRODUCTION

Breast cancer is the second-highest incidence in the world and the first among women, representing a major public health problem worldwide[1].

Extreme changes in the surgical approach to breast cancer have occurred significantly in recent years. Minimally invasive surgeries emerged thanks to advances in technology, which have helped oncological surgeons to operate on increasingly smaller lesions detected only in imaging tests[2].

In recent decades, nuclear medicine has become a great ally in the surgical field as a result of the development of the portable gamma radiation detector (gamma probe), which introduced studies based on the sentinel lymph node (SLN)[3], extending to the radioguided localization of non-palpable breast lesions (Radioguided Occult Lesion Localization), initially using radiopharmaceutical and, later, sealed sources of iodine-125, known as iodine-125 seeds[4,5]. More recently, hybrid tracers, which contain integrated radioactive and fluorescent markers, have been introduced to allow the detection of SLN[6,7]. Currently, the most promising tracers for this technique are considered to be colloids labeled with technetium-99m and indocyanine green (ICG).

ICG, which has been used since 1950[8], is a blood pooling agent that has a different delivery behavior between normal and cancer vasculature. In normal tissue, ICG acts as an indicator of blood flow in the narrow capillaries of normal vessels. However, in tumors, it can act with a diffusible (extravascular) flow caused by greater extravasation resulting from the increase in capillarity, thus intensifying the accumulation of the substance at the site[9].

This pilot study aims to describe the development of a new hybrid technique for marking and locating non-palpable lesions

[1]Centro de Diagnóstico por Imagem – Goiânia (GO), Brazil.
[2]Universidade Estadual Paulista, Faculty of Medicine of Botucatu – Botucatu (SP), Brazil.
[3]Santa Casa de Misericórdia de Goiânia – Goiânia (GO), Brazil.
[4]Hospital Estadual Alberto Rassi – Goiânia (GO), Brazil.
[5]Instituto de Mastologia e Oncologia – Goiânia (GO), Brazil.
[6]Universidade Federal de Goiás – Goiânia (GO), Brazil.
[7]Instituto Goiano de Oncologia e Hematologia – Goiânia (GO), Brazil.
[8]Universidade de São Paulo – São Paulo (SP) Brazil.
***Corresponding author:** dr.antoniocesar@yahoo.com.br
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and evaluating surgical margins in real time, called Fluorescence and Seed for Hybrid Intraoperative Evaluation (FLASHIE), using hybrid gamma probes to detect seed iodine-125 andICG.

METHODS

This is a cross-sectional, interventional pilot study with prospective data collection from patients with suspected or confirmed non-palpable breast cancer lesions between January and February 2018, after approval by the local Research Ethics Committee.

Seven patients over 18 years of age were included, one with a pre-operative diagnosis of benignity and the other six with a malignant biopsy, after signing the informed consent form.

The inclusion criteria were patients investigated by fine needle aspiration, core biopsy, or mammotomy, with an indication for radioguided lumpectomy. Patients with associated excisional biopsy, liver disease, uremia, asthma, a history of allergy to iodine or seafood, and previous anaphylactic reaction to dye injection were excluded from the study.

This is a convenience sample due to the restricted research development period of 1 month, when the researchers had the Europrobe Optonuclear equipment available for the work on loan from the manufacturer Eurorad in partnership with the commercial representative in Brazil, Eckert and Ziegler. Initially, the study was scheduled to last 3 months, but due to customs delays, it was restricted to 1 month.

Occult lesions were marked by implanting an iodine-125 seed in the center of each patient's breast lesion in a procedure guided by ultrasound (nodules) or stereotactic (microcalcifications) between 1 and 5 days before surgery. The correct apposition of the seeds was confirmed by mammographic images in two projections and planar scintigraphic images of the thoracic region in the anterior and lateral projections ipsilateral to the affected breast, acquired on the day of implantation or 1 day before surgery.

The seeds consist of a sealed titanium source of 4×1 mm in diameter with an iodine-125 filament included with 0.2 mCi activity and energy of 27–35 KeV (IPEN, São Paulo, Brazil). Scintigraphic images were captured in Symbia E (Siemens, Germany) or Millennium MG (General Electric, USA) gamma cameras with 500 Kctg, 256×256 matrix, photopeak centered at 30 keV, and ±10 keV window.

On the day of surgery, 30 min before the surgical intervention, 5 mg of ICG (ICV® Ophthalmos, São Paulo, Brazil) was injected intravenously. During surgical exploration, an optonuclear probe for open surgery (Europrobe 3.2 Optonuclear, Euromedical Instruments, Eckbolsheim, France) was used with the combination of a traditional gamma probe and a 769 nm narrowband laser excitation source to remove the tumor lesion (Figures 1 and 2). The probe was prepared with a sterile plastic cover to be handled by the mastologist.

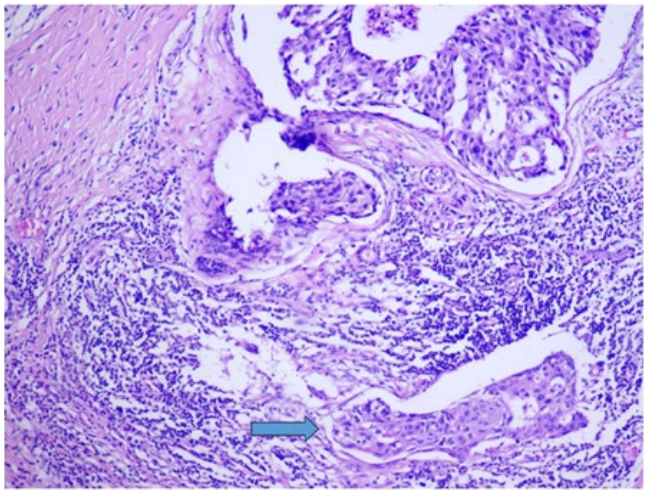

Figure 1. Anatomopathological study of the neoplastic area in the posterior region of the surgical bed (FI=15) after the removal of the primary lesion in patient 3. Color: H&E. Objective: 40×. The blue arrow indicates the presence of microinvasive carcinoma.

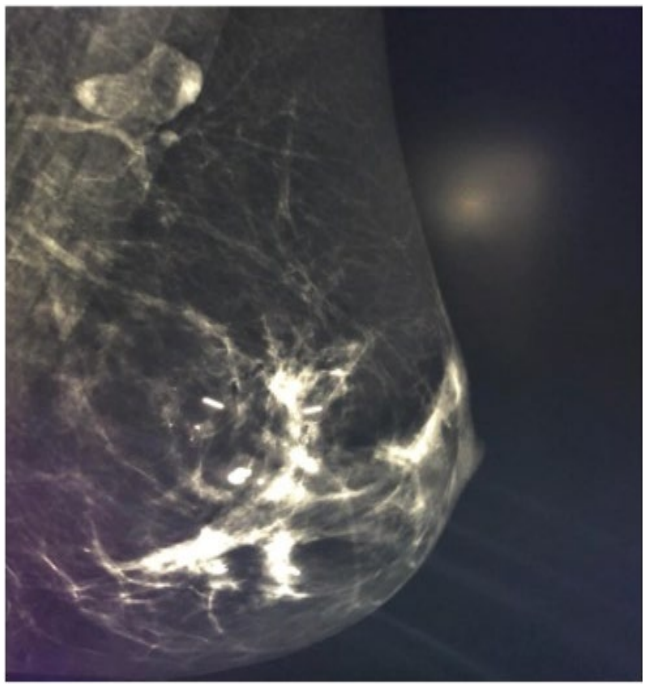

Figure 2. Mammography of patient 3 shows areas of microcalcifications marked by iodine-125 seed. No radiographically suspicious area was identified in the region posterior to the marked area.

During dissection, the lesion was localized initially, guided by the iodine-125 seed by the probe in conventional gamma-ray reading mode. Once the lesion was located, the probe's readout mode was switched to fluorescence. The areas defined in the preoperative images were analyzed by ICG fluorescence, and the reading was performed in ambient light.

Tumor fluorescence readings were performed intraoperatively (*in vivo*) and perioperatively (*ex vivo*). Once the lesion was removed, a new reading was performed at the margins of the lesion and in the tumor bed. A quantitative parameter was used to classify positivity for malignancy both in the primary lesion and in the surgical bed.

The fluorescence index (FI) was adopted, which consists of dividing the fluorescence count measured in the tumor by the fluorescence count measured in the healthy tissue surrounding the tumor and is considered positive when FI≥3, similar to that adopted in the study carried out by Duarte et al.[10] at the Universidade de Campinas – Brazil, in a technique called Radioguided Intraoperative Margin Evaluation, in which a radiopharmaceutical (^{99m}Tc-sestamibi) was also used during surgical procedures to check if the resection margins were negative.

The excised material was sent to the Pathology Service for cytology and freezing analysis by imprint. Part of the sample was submitted to a histopathological study, fixed by formalin and paraffin, and a late anatomopathological study (AP) by staining with hematoxylin and eosin. The specimen was also subjected to automated immunohistochemistry (IMHQ) with HIER PTLink antigen retrieval incubation and development in AUTOSTAINERLink48/DAKO.

The surgical specimens were generally classified based on the absence or presence of malignancy, whereas in this study, the cases were classified based on whether or not the margins and surgical bed were affected. For ethical reasons, the patients were named numerically.

RESULTS

Seven women, aged between 53 and 72 years (an average of 63.7 years), were included in this study. Seven lesions were removed, all guided by the radioactive seeds and located with the gamma probe. Most of them had a primary malignant lesion. Only one patient (n# 2) was confirmed as having a benign lesion (complex sclerosing papilloma), with FI=1. There was a predominance of nodular lesions, some with associated microcalcifications and in situ components. All primary malignant lesions presented FI≥3. Margins with a larger FI were malignant or small. ICG was more assertive than freezing in identifying compromised margins, based on AP. Table 1 presents this information.

Patient 3 presented FI=4 in the primary lesion, marked by iodine-125 seed, and in a deeper area, relatively distant from the marked area, FI=15 was measured. Due to the high FI, we opted for additional surgical expansion in this region. The AP confirmed malignancy. During the surgical procedure, in the frozen section, the margin of the enlarged region was considered compromised by the pathologist, so it was enlarged again, although there was no increase in the fluorescence reading in this surgical bed (FI=1).

Table 1. Correlation between the findings of fluorescence index, anatomopathological study/immunohistochemical study, and surgical margins of breast lesions.

Patient	Characteristics of the injury	Pathology	*In situ*	Local	FI	Freezing	AP/IMHQ	Assertiveness FI	Assertiveness freezing
1	Nodule	IDC GI* Luminal A	Not observed	Lesion	3	Malignant	Malignant	Yes	Yes
				Margin	1	Free	Free	Yes	Yes
2	Nodule	Complex sclerosing papilloma	Unrealized	Lesion	1	Benign	Benign	Yes	Yes
				Margin	NA	NA	NA	NA	NA
3	Nodule	Multifocal CDmI (3 foci) Hybrid luminal	Extensive (99.5% of the lesion)	Lesion	4	Malignant	Malignant	Yes	Yes
				Deep posterior region	15	Compromised	Compromised	Yes	Yes
				Margin	1	Compromised	Negative	Yes	No
4	Nodule	IDC GII* Luminal B	Scarce	Lesion	4	Malignant	Malignant	Yes	Yes
				Margin	1	Compromised	Free	Yes	No
5	Nodule	IDC Luminal A	Not observed	Lesion	7	Malignant	Malignant	Yes	Yes
				Posterior margin	6	Free	Exiguous	NA	No
6	Nodule + microcalcifications	IDC Luminal A	Extensive (>25% of the area)	Lesion	4	Malignant	Malignant	Yes	Yes
				Margin	1	Free	Free	Yes	Yes
7	Microcalcifications	IDC GII¶,‡‡ Luminal A	Extensive (99.5% of the lesion)	Lesion	4	NR	Malignant	Yes	NA
				Posterior margin	5	NA	Exiguous	NA	NA
				Margin	4	NR	NR	NR	NR

*Scarff-Richardson-Bloom. In situ: associated in situ component; FI: fluorescence index; AP: anatomopathological study; IMHQ: immunohistochemical study; IDC: invasive ductal carcinoma; GI: grade I; NA: not evaluated; CDmI: microinvasive ductal carcinoma; GII: grade II; NR: not carried out.

After the AP with paraffin, the frozen section study was re-read, and the posterior margin was retrospectively considered free, a result reinforced by the histopathological reading of the new margin enlargement, which was also negative for malignancy. Figures 1 and 2 show, respectively, AP confirming micro-invasive carcinoma and the absence of suspicion of malignancy on mammography at the site with FI=15.

Patient 7 presented a heterogeneous area with cysts, indistinct margins, with intervening calcifications and a posterior acoustic shadow in the left breast on imaging examination, and a core biopsy was performed. The AP identified fibrocystic mastopathy containing areas of usual ductal hyperplasia and an atypical 1.0 mm area. This dubious finding indicated the removal of the entire lesion.

During the location of the suspicious area, with the iodine-125 seed, the ICG reading showed FI=4 at the seed location and FI=5 at the posterior margin in the ex vivo measurement of the piece. The reading corresponding to this region on the surgical bed also measured FI=4. As there was no diagnosis of a malignant lesion yet, freezing was not performed. Although the margin presented FI≥3, the mastologist preferred not to enlarge this area, opting not to remove it and wait for the AP result.

In this case, invasive ductal mammary carcinoma, grade III (Scarff-Richardson-Bloom), with an extensive carcinoma in situ component, corresponding to 90% of the lesion, which measured 2.0×1.8 cm in its largest dimensions, with an invasive area of 0.7×0.5 cm and multifocal lobular cancerization, was present.

This result was confirmed by immunohistochemistry (IMHQ) as invasive mammary carcinoma, luminal A subtype. The margins were free but narrow in the posterior, medial, and inferior regions, so it was decided to investigate the sentinel lymph node without enlarging the margins.

Patient 4 had infiltrating breast carcinoma, grade II (Scarff-Richardson-Bloom), which during the surgical procedure indicated FI=4 in the lesion and FI=1 in the margins, that is, without identifying malignancy. Freezing showed compromised margins on the anterior and inferior surfaces, which indicated enlargement of the margins. The AP showed free margins, indicating a false-positive result for the frozen section and a true-negative result for the ICG evaluation.

Patient 5 had infiltrating breast carcinoma, grade II (Scarff-Richardson-Bloom) on core biopsy, and during the surgical procedure, she presented FI=7 in the lesion and a small area in the posterior region of the surgical bed with FI=6, which showed a small posterior margin (1.0 mm).

Patients 1 and 6 obtained, respectively, FI=3 and FI=4 in primary lesions and frozen-free margins, with FI=1, concordant findings.

DISCUSSION

Despite the low sample size of this pilot study, good results were obtained in the evaluation of this technique using hybrid marking. The assertiveness of ICG in primary tumor lesions was precise, distinguishing malignant from benign lesions.

It is clear that the series must be increased, since in the literature there is a description of false-positive results due to mastitis where there is increased microvascular permeability, which allows the extravasation of macromolecules, and also in epidermal cysts, the latter being an uncommon entity[11]. The diagnostic association with other investigation methods helps in differentiating these lesions.

Breast-conserving surgery via partial mastectomy is an increasingly used option in the treatment of patients with invasive or in situ carcinoma[3], but the assessment of margins can be difficult. Frozen freezing and AP are used to prevent residual disease after surgery and have an impact on the risk of breast tumor recurrence[2,12].

In this study, three of six patients presented an extensive in situ component in a large part of the lesion, which was marked by ICG. Hagen et al.[13] also reported the case of a patient in whom there were two nearby lesions, identified as well-differentiated invasive ductal carcinomas, accompanied by a low-grade ductal carcinoma in situ, which was evidenced on fluorescence mammography with ICG. The presence of multifocality was observed in patient 3. Perhaps, the extremely high FI present in the remaining tissue is associated with the secondary multifocal focus.

St. John et al.[14] concluded in their meta-analysis that the diagnostic accuracy of frozen section and cytology studies is currently unparalleled. According to these authors, to become a disruptive technology, emerging techniques will need to compete with this level of precision and provide significant improvements, such as speed of results, cost-benefit, and accessibility of information to the surgeon, to allow rapid operational decision-making, which must be accurate and appropriate. In this context, the ICG fluorescence technique could play an important role, as it evaluates the margin in real time.

The exact determination of the extent of breast carcinoma is increasingly important for the breast surgeon. If a technique underestimates the actual size of the lesion, it may lead the surgeon to a more conservative procedure, leaving residual disease, and, if overestimated, it may induce the removal of normal tissue, compromising the cosmetic aspect of the surgery.

Holland et al.[15] showed foci of carcinomas more than 2 cm away from the main tumor in 43% of cases and more than 4 cm in 10% of them. In the sample studied, although not identified by other imaging methods or frozen section studies, a distant neoplastic area was identified by the fluorescence technique when reading the surgical bed, making it possible to enlarge the margin in real time.

There were also two patients (5 and 7) who presented small margins, and the FI was high in their respective regions, favoring the good correlation of the technique with the changes seen in the AP, indicating that the clinical integration of these two powerful technologies, interventionalists with molecular imaging potential, can act in synergy and add important characteristics

of both techniques, including the ability to microscopically evaluate lesions and their margins, both in vivo and ex vivo[16,17].

Furthermore, the analysis of surgical margins can potentially be expanded to evaluate other organs and even use other fluorescent dyes, as reported by Xiao et al.[18], who used sodium fluorescein for fluorescent-guided surgeries for the excision of brain metastases from breast cancer.

Among the limitations of the study, the main one was the short period of availability of equipment for the project, which was scheduled for 3 months, but was carried out in 1 month due to bureaucratic problems with customs clearance, which directly impacted the sample size and, consequently, the development of research.

The small sample size, included for convenience, collected a heterogeneous sample of breast lesions, not allowing similar lesions to be grouped to investigate the existence of a pattern of accumulation of ICG and FI in different types of lesions. It seems that in multifocal and non-nodular lesions, the importance of using this technique is greater due to the limitations of other imaging techniques. New studies must be conducted to provide answers and evaluate the real impact of this technology on various breast injuries.

CONCLUSIONS

Within the limitations of the study, it was concluded that the proposed technique, FLASHIE, is feasible and quite promising. Preliminary results indicated the potential to advance the state of the art in cancer surgical techniques, with the possibility of accurate detection of occult primary lesions and an indication of residual disease after tumor removal, in real time, especially in those areas not detected by diagnostic techniques and management of margins already established.

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AUTHORS' CONTRIBUTION

ACP: conceptualization, data curation, investigation, methodology, resources, project administration, visualization, writing – original draft. SMM: data curation, investigation, writing – review & editing. MCD: data curation, formal analysis, investigation, validation, writing – original draft. RBF: data curation, methodology, research, validation, visualization. AMXJ: data curation, methodology, research, validation, visualization. DMC: investigation, validation, visualization. SAP: data curation, validation, visualization. JRB: data curation, investigation, validation, writing – review & editing.

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ORIGINAL ARTICLE
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Epidemiology of breast cancer in a tertiary oncology hospital in the countryside of Minas Gerais

Luiz Carlos Navarro de Oliveira[1], Sebastião Maurício de Oliveira Castro[2,3], Carla Simone Moreira de Freitas[4], Rita de Cássia de Jesus Duarte Silva[2], Flávio Ferraz Vieira[2], Rodrigo Bastos Tostes[5], Bruno Licy Gomes de Mello[6], René Aloisio da Costa Vieira[1,7,8*]

ABSTRACT

Objective: In Brazil, the characteristics of breast cancer patients who arrive at cancer treatment services are influenced by conditions related to the tumor, to the diagnostic system and navigation in the phase prior to care, with regional differences being little known as well as their seasonal variation. **Methods:** This is a retrospective study of epidemiological data of patients with breast cancer treated at the Hospital do Câncer de Muriaé (HCM), an exclusively oncology hospital (CACON II), with primarily public care, a reference for cancer treatment in the east of Zona da Mata region, Minas Gerais. Clinical and care-related characteristics were evaluated from 2010 to 2021. **Results:** During this period, 4,573 new patients were treated. The care was primarily public (80.5%) and most patients were undiagnosed (45.7%) or untreated (71.8%) at the first visit. The patients were between 40 and 69 years old (70.2%) and a significant portion were between 70 and 74 years old (7.4%). The rate of early stage (clinical stage – CS 0 + I) represented only 33.9 and 25.8% of all patients and those treated exclusively in the hospital, respectively. There was no change in clinical stage and age group over the years. **Conclusion:** When evaluating epidemiological data, the characteristics of the service and the pre-institutional diagnostic care network should be analyzed, facts that influence the results. Throughout the period, there was no great variation in relation to age group and staging. In this region, the early stage of breast cancer has unsatisfactory rates, and the 70 to 74 age group should be considered in mammographic screening. Epidemiological studies are essential to improve health strategies.

KEYWORDS: breast neoplasms; epidemiology; trends.

INTRODUCTION

Breast cancer is the main type of neoplasm in women in the world[1,2]. In developed countries, there is a high incidence and relative mortality, which is contrary to what occurs in developing countries, where it is possible to observe a lower incidence, but a higher mortality, which is influenced by the stage of diagnosis and treatment[2,3].

Breast cancer screening is associated with a decrease in mortality[4], due to the increase in the number of patients in the early stage, which reflects better survival[5]. In addition, the increase in the Human Development Index (HDI) has repercussions on the increase in patients with the initial clinical stage[6].

The early stage is sensitive to technology, thus requiring mammography, biopsy, and diagnostic flow. In Europe, mammography screening is a reality, and mammography is performed on a large scale in asymptomatic patients. Based on this concept, EUSOMA (European Society of Breast Cancer Specialists) created quality criteria for screening in Breast Units[7], but for places where mammographic screening is not a reality, mainly in developing countries, such as Brazil, services are focused on the demand for treatment, with few organized experiences[8,9]. To assess the quality of patients who arrive at the services, indirect indicators can be used, with the clinical stage being easily assessed in Brazil[6].

[1]Hospital de Câncer de Muriaé, Mastology Division, Department of Oncological Surgery – Muriaé (MG), Brazil.
[2]Hospital do Câncer de Muriaé, Hospital Cancer Registry – Muriaé (MG), Brazil.
[3]Hospital do Câncer de Muriaé, Head and Neck Division, Department of Oncological Surgery – Muriaé (MG), Brazil.
[4]Hospital do Câncer de Muriaé, Department of Clinical Oncology – Muriaé (MG), Brazil.
[5]Hospital do Câncer de Muriaé, Department of Radiotherapy – Muriaé (MG), Brazil.
[6]Hospital do Câncer de Muriaé, Infectious Diseases Division, Department of Medical Clinics – Muriaé (MG), Brazil.
[7]Universidade Estadual Paulista, Faculdade de Medicina de Botucatu, Graduate Program in Obstetrics and Gynecology – Botucatu (SP), Brazil.
[8]Fundação Pio XII, Hospital do Câncer de Barretos, Graduate Program in Oncology – Barreto (SP), Brazil.
***Corresponding author:** reneacv@gmail.com
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With a better understanding of breast cancer, it can be evaluated through molecular subtypes, a fact that influences treatment and is associated with age, diagnosis, ethnicity/skin color, and ancestry[10,11].

Hospital Cancer Registries are valuable sources for the evaluation of regional characteristics, age at diagnosis, clinical stage at diagnosis, treatment, and actuarial survival. In breast cancer, these data reflect on the quality of the healthcare service prior to the hospital unit. Unfortunately, few services have their data published[12-14]; these data allow to assess the quality of the public healthcare service prior to hospital admission.

The Hospital do Câncer de Muriaé (Muriaé Cancer Hospital – HCM) is an oncology hospital that preferably serves patients from the public health system, being a High Reference Center in Oncology *(Centro de Alta Complexidade em Oncologia* [Oncology Center of High Complexity] – CACON II),[15] located in Zona da Mata, in the countryside of Minas Gerais. It started its hospital activities in 2002 and the Hospital Cancer Registry (*Registro Hospitalar de Câncer* – RHC) only in 2010. There are no reports of epidemiological evaluation of breast cancer in this region, justifying an epidemiological study on this disease.

METHODS

This is an observational, retrospective study of data from the HCM's RHC from 2010 to 2021. The hospital is a public institution managed by the Fundação Cristiano Varela (Cristiano Varela Foundation), with primarily public care (85%), covering about 200 cities, with an estimated population of 3.1 million inhabitants. There is no other hospital or tertiary service in Oncology in this region of Minas Gerais.

The RHC data are public and can be accessed on the hospital's website (https://www.fcv.org.br/site*; Hospital; Registro Hospitalar de Câncer*), a fact that disregards the need for evaluation by a Research Ethics Committee, due to Resolution No. 466/2012. In addition, institutionally, the RHC authorized the analysis of the data. As the data change over time, the last evaluation, carried out on May 22, 2023, was used as a reference.

The authors sought to evaluate data exclusively related to breast cancer, in view of epidemiological characteristics and temporal variations related to clinical stage and age. In the evaluation of the clinical stage, the patients were classified as early stage (clinical stage – CS 0 and I), advanced stage (CS II and III), and metastatic stage (CS IV). The age group was divided into: under 40 years, 40–74 years, and over 74 years.

Figures were created by IBM SPPS for Mac version 22.0 (Figure 1) and Excel for Mac version 16 (Figure 2 and 3). Decimal numbers were automatic separated automatic in comma and not point.

RESULTS

We observed an increasing rise in the number of patients, potentially associated with the increase in the number of referenced cities. The care was primarily public (80.5%), patients from cities in Minas Gerais (94.3%); most patients were undiagnosed (45.7%) or untreated (71.8%) at the first visit, had a low level of education (62.8% up to elementary school), and were married (55.2%) (Table 1).

The patients were generally brown (47.7%), aged 40–69 years (70.2%) (Figure 1), and native of Minas Gerais (81.1%). Attention should be given to the 70–74 years age group because there are controversies regarding screening, representing 7.4% of tumors (Table 2).

The main histological type identified was invasive ductal carcinoma (80.1%), followed by invasive lobular carcinoma (7.9%). Carcinoma ***in situ*** was present in 6.0% of the patients; only 33.9% had an early clinical stage (CS 0 + I). When evaluating only the cases initially treated at the hospital, 5.4% of the patients had CS 0, and 25.8% had an early stage (Table 2).

In addition, we evaluated the main characteristics of the patients treated by the Brazilian Unified Health System (SUS) in relation to the private system (Table 3): most of the patients without a diagnosis were from the SUS (47.2%), while in the private system, most patients already had a previous diagnosis ($p<0.001$). The clinical stage was also influenced by the type of care: patients with early stage (0 + I) came mainly from the private system (31.1% *versus* 26.2%; $p<0.001$). The patient's age was not influenced by the care system.

With the temporal evaluation, we observed, over the years, the maintenance of the age group at diagnosis and the clinical stage, and a small increase in the number of patients with clinical stage IV in the years of the new coronavirus (Covid-19) pandemic (Figures 2 and 3).

DISCUSSION

The literature is limited with regard to epidemiological data on breast cancer-related RHC. There are experiences of cancer hospitals[12], oncology units[14,16], Specialty Reference Centers[17,18], and the Regional League[19]. When evaluating epidemiological data related to breast cancer, derived from hospitals or reference services, the regional characteristics, the referral flow, the existence of other services in the region, and the characteristics of the accreditation of the oncology unit should be analyzed, a fact that may impact the presented results. The HCM serves a region referenced in the east of Zona da Mata where there is no other Oncology unit, public or private, constituting itself as a regional reference for cancer treatment. It is established as a CACON II Hospital[15], as it contains all types of treatment related to cancer care, from diagnosis to palliative care, with a high rate of resolution.

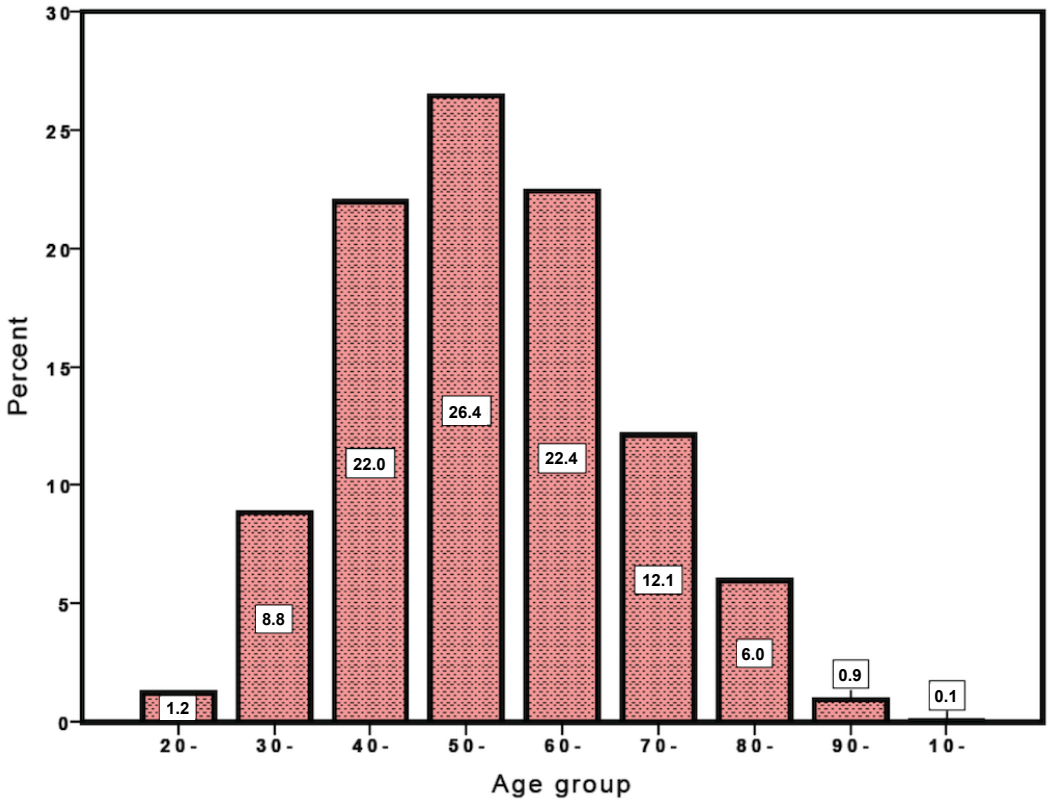
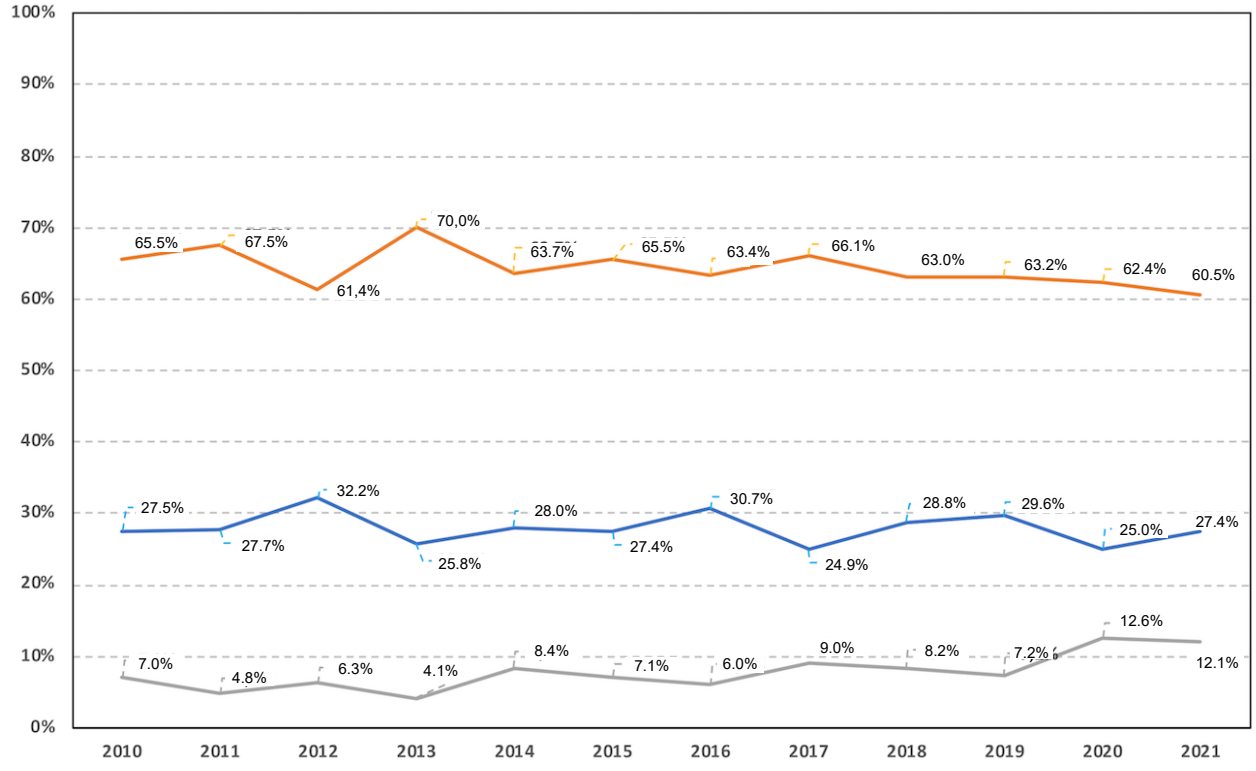


Figure 1. Age distribution.



CS: clinical stage; Early: CS 0 and I; Advanced: CS II and III; Metastatic: CS IV.

Figure 2. Time curve from the clinical stage (%) to diagnosis.

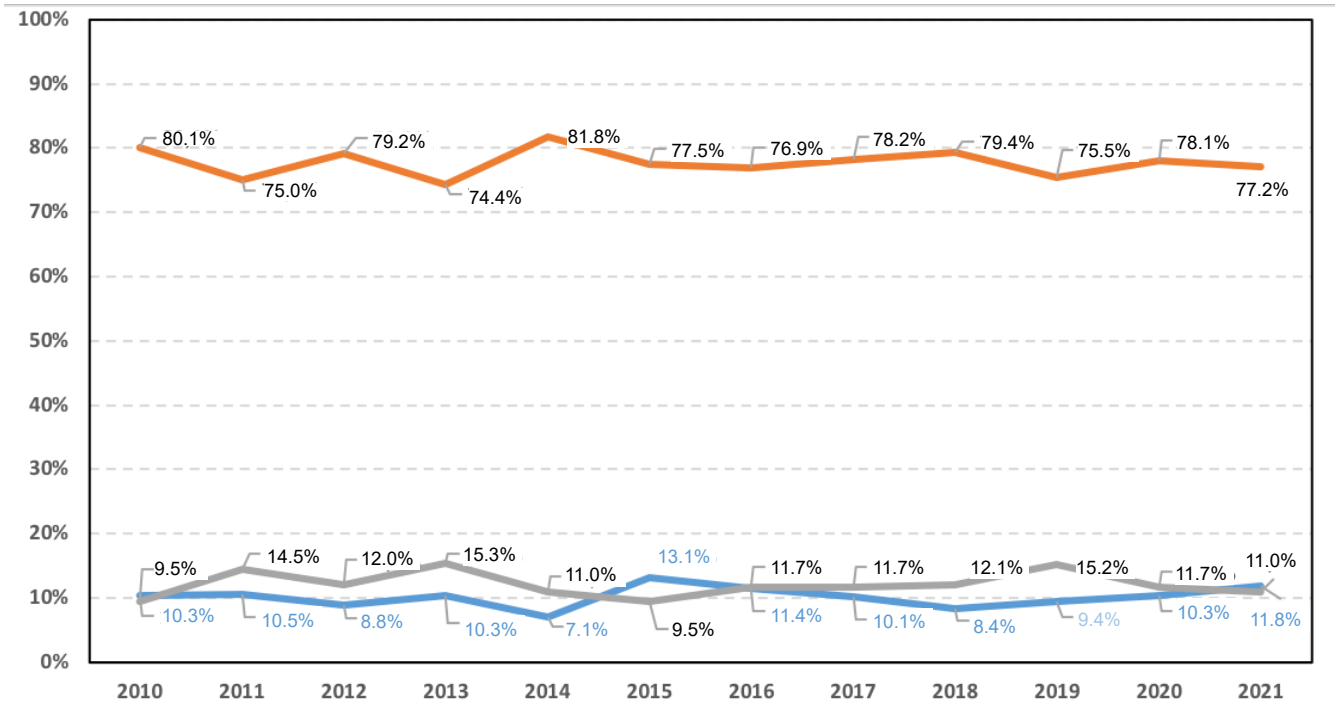


Figure 3. Time curve of the distribution of the age group at diagnosis

We observed an increasing rise in the number of patients, a fact that reflects the efficiency and organization of the cancer treatment network. Historically, the hospital served patients from other nearby states, a fact that has changed over time — currently, care is exclusive to patients from the state of Minas Gerais. As for breast cancer, since 2010 there has been an increase in the annual rate, which ranged from 259 women in the first triennium to 492 women in the last triennium. The HCM is a public hospital, privately managed, preferably serving SUS patients (80.5%), and private care is limited (13.1%).

With regard to breast cancer, the main access for patients is through the Mastology Division and Clinical Oncology sectors. Initially, Mastology was served together with Oncological Surgery, a fact that was modified due to the growth and the need for a team dedicated to this specialty. The inclusion of patients in the Mastology Division occurs due to the high suspicion lesions or confirmation of neoplastic disease, and patients with BI-RADS 4 and 5 lesions or confirmed breast neoplasms are evaluated. Due to limitations in the regional health system, many suspected cases are diagnosed at the hospital level. The structuring and resolution of the regional healthcare system have an impact on the type of referred patient, and there is also a high rate of patients who need complementary diagnostic evaluation and diagnostic breast biopsy. When assessing breast cancer, 45.7% of the patients were diagnosed at the institution, 26.1% arrived with a diagnosis and without treatment, and 27.4% had already undergone some type of oncological treatment.

Assessing patients' age characteristics is essential to understand potential changes related to risk factors as well as screening strategies. The Brazilian Ministry of Health suggests that screening should be carried out in the age group of 50 to 69 years, which would benefit 49.2% of patients. The Brazilian Society of Mastology (*Sociedade Brasileira de Mastologia* – SBM), in turn, suggests starting it at 40 years of age, which would benefit 70.2% of patients. The age group of 70–74 years represents about 7.4% of patients. When evaluating the Brazilian population pyramid, there is a gradual decrease in the number of patients according to age group, and a significant number of patients in the age group of 70–74 years was observed, a fact that should be taken into account, especially in relation to those with high life expectancy, as suggested by the SBM.

Comparing the age groups, we observed no changes in the analyzed period, nor any differences in age group and clinical stage in patients from the public or private systems. Another factor that can influence the age group is the hospital characteristic. Private hospitals, which depend on health insurance plans, may have a younger population with higher income, which is associated with the availability of resources to maintain the health insurance — this fact must be better evaluated. The rate of patients under 50 years of age was 40% in a private hospital in the city of São Paulo[12] and 31.2% in the study's hospital.

The quality and care in staging is reflected in the quality of the RHC data. In this sample, 8% of data were ignored, and levels lower than 10% were acceptable. Another important finding is the rate of patients with stage IV, which is usually less than 10% — higher rates reflect serious limitations in the healthcare system. As it is an oncology hospital, 7.4% of the patients were diagnosed at this stage, a result influenced by the characteristics of the service, similar to that observed in oncology hospitals12,13 and oncology units14,16 (5.3% to

Table 1. General information on breast cancer patients treated at the Hospital do Câncer do Muriaé (MG).

Variable	Category	Number	%
Year of diagnosis	2010 to 2012	777	17.0
	2013 to 2015	1,023	22.4
	2016 to 2018	1,295	28.3
	2019 to 2021	1,478	32.3
Location	Minas Gerais	4,315	94.3
	Rio de Janeiro	246	5.4
	Espírito Santo	12	0.3
Type of service	Brazilian Unified Health System	3,682	80.5
	Health insurance	576	12.6
	Private	70	1.5
	Other	245	5.4
Clinic – admission*	Mastology	1,772	38.7
	Clinical oncology	1,578	34.5
	Radiotherapy	487	10.6
	Surgical oncology	480	10.5
	Other	14	0.4
Place of origin – birthplace	Southeast – Minas Gerais	3,708	81.1
	Southeast – other states	777	17.0
	Northeast	59	1.3
	South	18	0.4
	North	7	0.2
	Midwest	4	0.1
Level of education	Absent	345	7.5
	Some elementary school	2,031	44.4
	Elementary school	499	10.9
	High school	901	19.7
	College degree	606	13.3
	No information	191	4.2
Marital status	Single	1,017	22.2
	Married	2,524	55.2
	Common-law marriage	25	0.5
	Divorced	436	9.5
	Widow(er)	571	12.5
Total	–	4,573	100.0

*Patients initially treated at another institution were excluded from this study.

8.0%), and lower than that observed in regional outpatient reference centers17,18. In a national study whose authors evaluated only invasive tumors, the national rate was 9.3%20. At the HCM, during the Covid-19 pandemic, there was an increase in the number of patients with stage IV, reaching 12.1%, a fact potentially influenced by serious limitations in patient navigation at the care level prior to hospitalization21.

Another factor associated with the quality of services is the rate of patients with early stages (CS 0 + I)9: 25.8%. Stage zero corresponds to carcinoma ***in situ***, usually diagnosed by mammographic screening, evidencing the impact of this test as a diagnostic tool for breast cancer. In a place with organized screening, in a small city of the State of São Paulo, Brazil, three phases were observed: prior to screening (CS 0 + I = 13%); in the

Table 2. Data related to presentation at hospital admission.

Variable	Category	Number	%
Sex	Women	4,551	99.5
	Men	22	0.5
Ethnicity/skin color	Brown	2,183	47.7
	White	1,841	40.3
	Black	526	11.5
	Asian	4	0.1
	Ignored	19	0.4
Age group (years)	<40	466	10.2
	40–49	962	21.0
	50–59	1,227	26.8
	60–69	1,023	22.4
	70–74	339	7.4
	≥75	556	12.2
Diagnosis	ND, NT	2,091	45.7
	WD, WT	1,192	26.1
	WD, WT	1,254	27.4
	Other	36	0.8
Histological type	IDC	3,662	80.1
	ILC	359	7.9
	DCIS	213	4.7
	Other	339	7.3
CS–TNM*	CS 0	251	6.0
	CS I	921	27.9
	CS II	1,625	38.6
	CS III	1,066	25.3
	CS IV	343	8.2
CS–TNM†	CS 0	168	5.4
	CS I	639	20.4
	CS II	1,245	39.7
	CS III	854	27.2
	CS IV	231	7.4

ND: no diagnosis; NT: no treatment; WD: with diagnosis; WT: with treatment; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; DCIS: ductal carcinoma in situ; CS: clinical stage. *Ignored data were excluded (n=367; 8%); †ignored data and data on patients with previous treatment were excluded.

first two years of mammographic screening (43.3%); and after consolidation of screening (60%), in which asymptomatic patients had better rates of early stage (84.3% *versus* 31.9%)[22,23]. At an oncology hospital in Curitiba (state of Paraná, Brazil)[13], from 2000 to 2009, this rate was 14.3%, but the rate of incomplete data was 16.9% and the study did not present numerical data, making it difficult to evaluate absolute data. In a private oncology hospital in the state of São Paulo[12], this rate was 46.7%. If the numbers were evaluated by the HDI, we would have, in descending order: Curitiba/State of Paraná (HDI = 0.823) > São Paulo/State of São Paulo (HDI = 0.805) > Barretos/State of São Paulo (HDI = 0.798) > Muriaé/State of Minas Gerais (HDI = 0.734). It is observed that the HDI is important, but it is also relevant how it actually reaches the SUS population, through health initiatives. Different results are observed depending on the presence and structure of the screening program, location, type of population served, and hospital characteristics. By comparing the numbers, we can observe the need to improve the regional public health system, the importance of organized mammography screening, and the need for improvements in the navigation of patients in the diagnosis of breast cancer in the SUS.

Table 3. Patient characteristics in relation to patient type*.

		SUS (%)	Private (%)	Total (%)	p-value
Type of Diagnosis	ND–NT	1,335 (79.0)	355 (21.0)	1,690 (42.9)	<0.001
	WD–WT	745 (71.5)	300 (28.5)	1,052 (26.7)	
	WD–WT	728 (61.1)	445 (37.9)	1,173 (29.8)	
	Other	11 (44.4)	14 (56.0)	25 (0.6)	
Age group (years)	<40	270 (68.0)	127 (32.0)	397 (10.1)	0.419
	40–49	603 (72.1)	233 (27.9)	836 (21.2)	
	50–59	758 (71.6)	300 (28.4)	1,058 (26.9)	
	60–69	644 (73.7)	230 (26.3)	874 (22.2)	
	70–74	215 (72.4)	82 (27.6)	297 (7.5)	
	≥75	336 (70.3)	142 (29.7)	478 (12.1)	
Clinical stage	CS 0	158 (74.5)	54 (25.5)	212 (5.8)	0.001
	CS I	532 (67.1)	261 (32.9)	793 (21.8)	
	CS II	1,013 (72.4)	386 (27.6)	1,399 (38.4)	
	CS III	717 (76.4)	221 (23.6)	938 (25.7)	
	CS IV	213 (70.3)	90 (29.7)	303 (8.3)	
Total		2,633 (72.2)	1,012 (27.8)	3,645 (100)	

SUS: Brazilian Unified Health System; ND: no diagnosis; NT: no treatment; WD: with diagnosis; WT: with treatment. *Patients whose origin is ignored were excluded from this study.

Authors of the Amazona III Study[24] evaluated patients with stages I to IV, coming from public and private services. When comparing the public and private systems, differences were observed in stages I, II, and IV: there was a higher rate of patients with stage I in the private service (40.6% *versus* 18.5%), and the diagnosis in this sector was mainly made by screening (53.0% *versus* 23.1%); there were no differences in relation to age group.

HCM has mixed characteristics, with partial private care. Patients from the private system generally arrived at the hospital with a confirmed diagnosis and/or previous treatment, with a higher rate of early clinical stage (31.1% versus 26.2%, compared to rates of patients treated by the SUS). This fact corroborates previous studies whose authors compared the public and private systems, but these numbers are lower than the rate of 46.7% observed in a private cancer hospital in São Paulo, which makes us ponder that other local cultural factors and adherence to mammography may influence the observed results. Another analyzed factor was age, which was not influenced by the preferred type of care at the hospital unit, in which there is a high rate of patients with health insurance from the Civil Servants of Minas Gerais.

Recently, there have been experiments showing associated numbers of hospital records[25], represented by newsletters; however, such data, usually raw, need to be better analyzed and contextualized. Likewise, the results should be compared over time in order to assess seasonal changes, such as the COVID-19 pandemic, or those associated with the structuring of the health system.

Thus, the main characteristics of our service were presented, with the limitations of the use of raw data, the lack of evaluation of molecular subtypes and survival, which can be presented in future studies.

CONCLUSIONS

When observing patients treated in the Zona da Mata, in the countryside of Minas Gerais, in a tertiary oncology hospital, there are also limitations associated with diagnosis in the public service; the hospital still provides secondary care, due to the high number of cases still diagnosed at the institutional level.

AUTHORS' CONTRIBUTION

LCNO: Data curation, Formal Analysis, Visualization, Writing – original draft, Writing – review & editing. SMOC: Data curation, Visualization, Writing – original draft, Writing – review & editing. CSMF: Data curation, Visualization, Writing – original draft, Writing – review & editing. RCJDS: Data curation, Visualization, Writing – original draft, Writing – review & editing. FFV: Formal analysis, Visualization, Writing – original draft, Writing – review & editing.

RBT: Data curation, Visualization, Writing – original draft, Writing – review & editing. BLGM: Visualization, Writing – original draft, Writing – review & editing. RACV: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Breast cancer and public healthcare: survey and proposals from Brazilian Society of Mastology (SBM)

Augusto Tufi Hassan[1], Jordana de Faria Bessa[2]*, Guilherme Garcia Novita[3], Sandra Gioia[4], André Mattar[3,5], Francisco Pimentel Cavalcante[6], Ruffo Freitas-Junior[7], Carlos Alberto Ruiz[8]

ABSTRACT

Introduction: High rates of breast cancer mortality have been reported for patients from public healthcare, in Brazil. This study aimed to obtain a panorama of breast cancer in public healthcare, based on a questionnaire sent to breast specialists. **Methods:** Active members of the Brazilian Society of Mastology (SBM) were invited to participate anonymously, from Aug-Oct 2023. Possible answers ranged from "This is not a problem" to "This is a very serious, very common problem". The primary endpoint of the study was the relative frequency of the answers. **Results:** Overall, 767 (44% of all SBM affiliated members) completed the questionnaire. Access to modern drugs was considered the most concerning problem, with 81.36% of respondents classifying this as "serious, frequently" or "very serious, very frequently", followed by access to diagnostic methods (64.53%), access to breast reconstruction (60.24%), delay in starting treatment (60.11%) and access to screening (51.76%). **Conclusions:** This is the first study to evaluate the perceptions of breast specialists on breast cancer care within SUS. The SBM has issued considerations and proposals aimed at reestablishing a minimally adequate standard of breast cancer diagnosis and treatment in public healthcare in Brazil.

KEYWORDS: public health surveillance; breast neoplasms; healthcare disparities; health inequities; socioeconomic factors.

INTRODUCTION

Approximately 72% of the Brazilian population relies exclusively on the public healthcare system (*Sistema Único de Saúde* – SUS) for medical care. The remaining population relies on a variety of healthcare insurance plans offered by private companies[1].

In oncology, there is currently an unprecedented crisis of inequality in the quantity and quality of care provided within the public healthcare sector compared to the private sector. Among women with breast cancer who depend on the public healthcare sector, disease-related mortality rates are particularly high[2,3]. The issues that contribute to this inequality are mostly related to screening and treatment[4,5].

The objective of the present study was to obtain a comprehensive overview of breast cancer care in public healthcare in Brazil through a questionnaire sent to breast specialists across the country.

METHODS

Study population

This online survey was conducted between August and October 2023. All 1,759 breast specialists affiliated with the Brazilian Society of Mastology (*Sociedade Brasileira de Mastologia* – SBM) were invited to participate anonymously in the study. Invitations to visit the web page hosting the questionnaire were sent via e-mails and messages, restricted to affiliates. Access to the questionnaire was not attached to any identification, e-mail, or personal contact. Non-respondents either did not visit the webpage, did not answer, or did not complete the questionnaire. An estimation of non-respondents was made, comparing data from the total number of SBM affiliates.

[1]President at Brazilian Society of Mastology – Salvador (BA), Brazil.
[2]Instituto D'Or de Ensino e Pesquisa – São Paulo (SP), Brazil.
[3]Oncoclínicas Group – São Paulo (SP), Brazil.
[4]Secretaria Estadual de Saúde do Rio de Janeiro – Rio de Janeiro (RJ), Brazil.
[5]Hospital da Mulher – São Paulo (SP), Brazil.
[6]Hospital Geral de Fortaleza – Fortaleza (CE), Brazil.
[7]Universidade Federal de Goias, Centro Avançado do Diagnóstico da Mama, Araújo Jorge Cancer Hospital, Program in Breast Diseases and CORA – Goiânia (GO), Brazil.
[8]Universidade de São Paulo – São Paulo (SP), Brazil.
***Corresponding author:** jordana.bessa@gmail.com
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Intervention

The online questionnaire consisted of eight objective questions:

- In which state do you live?
- How big is the population of the city/town in which you live or work?
- How is the situation regarding breast cancer screening within public healthcare where you live or work?
- How is the situation regarding delays in initiating breast cancer treatment in public healthcare where you live or work?
- How is the situation regarding breast reconstruction in the public healthcare where you live or work?
- How is the situation regarding breast cancer diagnostic methods (imaging, pathology, and genetic testing) in public healthcare where you live or work?
- How is the situation regarding treatment modalities such as access to targeted drug therapy, cyclin-dependent inhibitors, and immunotherapy in public healthcare where you live or work?

For each question, the possible answers were:

- I don't know
- This is not a problem
- This is a minor, infrequently occurring problem
- This is a moderate, occasionally occurring problem
- This is a serious, frequently occurring problem
- This is a very serious, very frequently occurring problem

Endpoints

The primary outcome of the study was the relative frequency of the answers to each question. The secondary outcome was the relative frequency of *"serious, frequently"* and *"very serious, very frequently"*, according to region and state.

Statistical analysis

This is a descriptive study without comparative analyses. Qualitative variables are expressed as relative frequencies. Tables, figures and maps were built with Microsoft® Excel.

RESULTS

A total of 767 breast specialists answered the questionnaire, representing 44% of all the physicians affiliated with SBM (Table 1). All respondents completed the questionnaire. The only state without representation was Acre.

Access to modern drugs was the most concerning problem, with 81.36% of respondents classifying it as a "*serious, frequently*" or "*very serious, very frequently*" problem, followed by access to diagnostic methods (64.53%), access to breast reconstruction (60.24%), delay in starting treatment (60.11%), and access to screening (51.76%) (Table 2). The proportion, by state, of answers "*serious*" and "*very serious*", is represented in Figures 1-3.

DISCUSSION

This is the first study to evaluate how breast specialists perceive the major problems involved in breast cancer control within the public healthcare system. The survey addressed five aspects: access to screening, delays in initiating treatment, access to breast reconstruction, access to diagnostic methods, and access to modern treatment modalities such as targeted drug therapy, cyclin-dependent kinase inhibitors, and immunotherapy. The aspect that was considered most concerning was the lack of access to modern drugs.

The issues that contribute to this inequality are mostly related to screening and treatment. Screening in Brazil is opportunistic, and highly dependent on adherence, which is historically

Table 1. Characteristics of the breast specialists from Sociedade Brasileira de Mastologia: respondents and non-respondents.

State	Respondents n (%)	Non-respondents n (%)	Total
Acre	0 (0)	2 (100)	2
Alagoas	8 (42)	11 (58)	19
Amazonas	8 (50)	8 (50)	16
Amapá	2 (40)	3 (60)	5
Bahia	43 (39)	67 (61)	110
Ceará	28 (45)	34 (55)	62
Distrito Federal	23 (36)	41 (64)	64
Espírito Santo	11 (50)	11 (50)	22
Goiás	21 (36)	38 (64)	59
Maranhão	7 (26)	20 (74)	27
Minas Gerais	96 (48)	102 (52)	198
Mato Grosso do Sul	8 (57)	6 (43)	14
Mato Grosso	7 (54)	6 (46)	13
Pará	9 (31)	20 (69)	29
Paraíba	13 (33)	26 (67)	39
Pernambuco	28 (49)	29 (51)	57
Piauí	11 (61)	7 (39)	18
Paraná	29 (39)	45 (61)	74
Rio de Janeiro	46 (37)	80 (63)	126
Rio Grande do Norte	16 (43)	21 (57)	37
Rondônia	1 (14)	6 (86)	7
Roraima	1 (50)	1 (50)	2
Rio Grande do Sul	41 (35)	76 (65)	117
Santa Catarina	29 (35)	54 (65)	83
Sergipe	4 (20)	16 (80)	20
São Paulo	273 (52)	257 (48)	530
Tocantins	4 (44)	5 (56)	9
Total	767 (44)	992 (56)	1759

Table 2. Main problems in public health according to the breast specialists who completed the questionnaire

Answer to Question	Access to screening n (%)	Delay in initiating treatment n (%)	Access to breast reconstruction n (%)	Access to diagnostic methods n (%)	Access to modern drugs n (%)
I don't know	24 (3.13)	18 (2.35)	28 (3.65)	12 (1.56)	44 (5.74)
This is not a problem	15 (1.96)	10 (1.30)	42 (5.48)	11 (1.43)	5 (0.65)
This is a minor, rarely occurring problem	67 (8.74)	74 (9.65)	79 (10.30)	61 (7.95)	25 (3.26)
This is a moderate, occasionally occurring problem	264 (34.42)	204 (26.60)	156 (20.34)	188 (24.51)	69 (9.00)
This is a serious, frequently occurring problem	298 (38.85)	287 (37.42)	208 (27.12)	274 (35.72)	177 (23.08)
This is a very serious, very frequently occurring problem	99 (12.91)	174 (22.69)	254 (33.12)	221 (28.81)	447 (58.28)

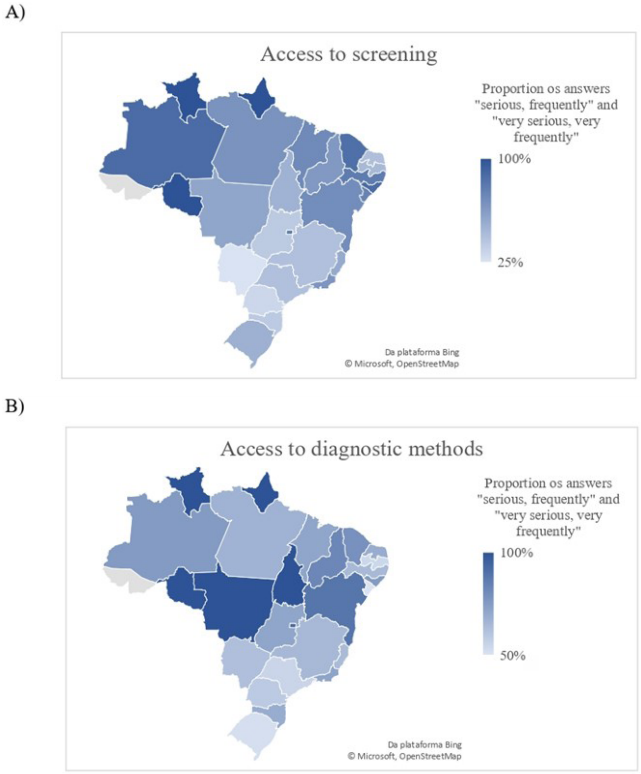

Figure 1. Perceptions as "*serious, frequently*" and "*very serious, very frequently*", regarding screening (A) and diagnostic methods (B), by state, according to breast specialists.

low[6]. Mammography coverage is estimated to reach only 30% of women[7]. Women in public healthcare are less likely to be diagnosed at stage 1[4]. After undergoing mammography, women then experience difficulty in accessing diagnostic tests. Comparing the number of biopsies and mammograms performed within the public healthcare system suggests that only 16.8% of biopsies are carried out within SUS[5,8]. The difficulty in scheduling a biopsy within SUS forces many women to undergo the procedure in private healthcare services.

There is an inverse association between the time interval until initiating treatment and a better breast cancer prognosis.

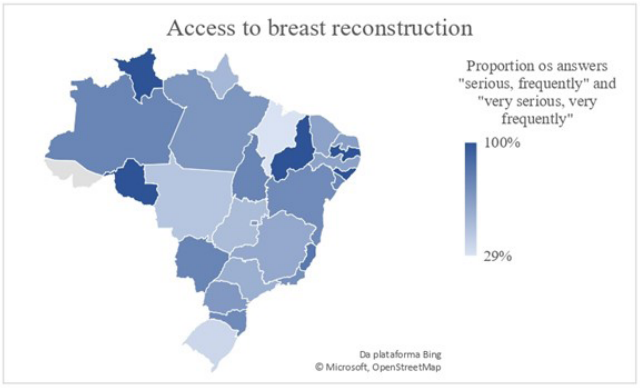

Figure 2. Perceptions as "*serious, frequently*" and "*very serious, very frequently*", to breast reconstruction, by state, according to breast specialists.

Ideally, time for surgery should not exceed eight weeks[9]. In relation to systemic treatment, a systematic review with meta-analysis showed that for every four weeks of delay, there is a reduction in overall survival and disease-free survival[10]. In Brazil, despite legislation that limits the initiation of treatment to 60 days, recent data show that the median waiting time is 59 days, with 49% of women waiting longer than that for treatment to begin[5].

Few data are available on access to breast reconstruction in Brazil. Although national legislation approved in 1999 guarantees the right to breast reconstruction, the number of surgeries performed is low. Studies estimate that only 20–29% of women who have undergone mastectomy within the public healthcare system are able to access breast reconstruction[11,12]. The causes are manifold and may include a lack of public service inspection, non-existent infrastructure, shortage of materials, and lack of trained surgeons. A study found that 20% of breast specialists had received no training in breast reconstruction during medical residency[13].

Currently, there are numerous unmet needs in breast cancer treatment within the SUS. Molecular testing to forecast the benefit of chemotherapy is unavailable, as is genetic testing.

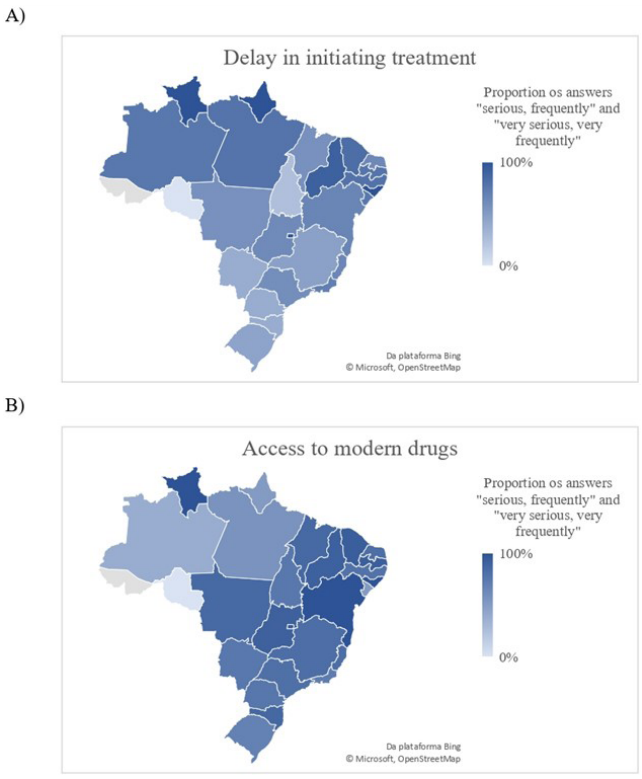

Figure 3. Perceptions as "*serious, frequently*" and "*very serious, very frequently*", to delay in initiating treatment (A) and access to modern drugs (B), by state, according to breast specialists.

The Ministry of Health's most recent updated Guidelines on the Diagnosis and Treatment of Breast Cancer does not include ovarian suppression, pertuzumab for cases of early breast cancer in neoadjuvant setting, cyclin-dependent kinase inhibitors, PARP inhibitors for early or metastatic breast cancer, or immunotherapy[14]. Some public hospitals offer treatment that is even inferior to those minimum recommended guidelines[15].

This is the first study to evaluate the perceptions of breast specialists, distributed throughout most of the country, on the problems associated with breast cancer treatment within the Brazilian public healthcare system. A limitation of the study is that the survey consisted of interviews that were dependent on individual perceptions rather than on primary data obtained from patients. Nevertheless, the present study should serve as an alert to this unprecedented crisis in the public healthcare sector.

SBM has issued the following considerations and proposals aimed at reestablishing a minimally adequate standard of breast cancer diagnosis and treatment within SUS:

1. *Compliance with legislation 14,335 of 2022 that establishes a lower limit of 40 years as the age at which to initiate breast cancer screening in Brazil, with mammograms to be performed annually thereafter.* We recommend a review of the Ministry of Health's recommendations on initiating screening at 50 years of age, with mammograms to be performed once every two years. The incidence of cancer in individuals under 50 years of age is increasing worldwide[16]. In Brazil, in particular, the proportion of cases in young women is high[17,18]. Epidemiological studies have shown that the onset of cancer risk occurs ten years earlier in black women compared to white women[19], who were underrepresented in screening trials. These are, in fact, the reasons why the United States Preventive Services Task Force changed its recommendation, reducing the age at which to start breast cancer screening from 50 to 40 years[20].
2. *Compliance with legislation 12,732 of 2012, which determines a maximum delay of 60 days until initiating treatment within SUS.* Delays in initiating treatment affect prognosis and entail more aggressive treatment, also resulting in financial toxicity[9].
3. *Compliance with legislation 9,797 of 1999, which requires corrective breast reconstruction surgery to be offered within SUS in cases of mutilation resulting from cancer treatment.* Likewise, it is paramount to ensure that cancer centers have a breast reconstruction team.
4. *Establishing equivalence between the procedures approved by ANVISA in the National Commission for the Incorporation of Technology within the National Health Service (Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde – CONITEC) and the National Agency of Supplementary Healthcare (Agência Nacional de Saúde Suplementar – ANS) with respect to diagnostic methods and treatment modalities.* Strategies must be drawn up to enable the incorporation, acquisition and adequate remuneration of diagnostic methods, including germline genetic testing, positron emission tomography (PET), breast magnetic resonance imaging (MRI), and vacuum-assisted biopsy. Likewise, modern treatment modalities should be incorporated, particularly trastuzumab emtansine (approved by CONITEC but still not available in SUS), cyclin-dependent kinase inhibitors (approved by CONITEC but still not available in SUS), pertuzumab (approved but available exclusively for cases of metastatic disease), pembrolizumab, trastuzumab deruxtecan, PARP inhibitors, goserelin, and sacituzumab govitecan.

CONCLUSION

This study shows how breast specialists perceive major problems involved in breast cancer control within public healthcare system in Brazil. Lack of access to modern treatment modalities was considered the most concerning aspect, followed by access to diagnostic methods, access to breast reconstruction, delay in starting treatment and access to screeening. Breast specialists are concerned that their SUS patients could be receiving insufficient screening and treatment. An agenda to deal with rising rates of breast cancer mortality should be drawn up without delay.

AUTHORS' CONTRIBUTION

ATH: Conceptualization, Supervision, Visualization, Writing – original draft. JFB: Formal analysis, Methodology, Software, Visualization, Writing – original draft. GGN: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – review & editing. SG: Validation, Visualization, Writing – review & editing. AM: Formal analysis, Visualization, Writing – review & editing. FPC: Formal analysis, Visualization, Writing – review & editing. RFJ: Conceptualization, Data curation, Supervision, Visualization, Writing – original draft. CAR: Supervision, Validation, Visualization, Writing – review & editing.

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Immediate reconstruction with implant post-mastectomy with prepectoral versus submuscular technique: experience of a public oncological treatment center

Pedro Lima Costa[1], Yara Carolina Monte de Sena Rosa[1], Gláucia Mesquita Cordeiro[1], Ana Gabriela Caldas Oliveira[2], Raquel Aranha Viegas[1], José Pereira Guará[1,2]*

ABSTRACT

Introduction: Reconstruction techniques after mammary adenectomy with implant placement in the prepectoral space without the use of cell dermal matrix have been attracting more interest recently. However, data on the risk of complications, especially in patients treated in Brazil by the Brazilian Unified Health System, are scarce. **Methods:** This is a retrospective cohort study on women who underwent mammary adenectomy and immediate reconstruction with implants in a public hospital in Brazil, with survival analysis for implant extrusion and its associated factors. **Results:** Prepectoral and submuscular implant-based reconstruction had similar clinical outcomes. High axillary involvement (four or more lymph nodes) was the only factor associated with implant extrusion, regardless of the implant reconstruction techniques used. **Conclusions:** Tumor burden might interfere with the immediate implant-based breast reconstruction.

KEYWORDS: breast cancer; breast implants; oncoplasty.

INTRODUCTION

Breast cancer is the disease that most affects women in the world. About one million cases are diagnosed per year[1]. In Brazil, there are approximately 73,610 new cases per year, with an estimated risk of 73.61 cases per 100 thousand women[2].

Breast cancer treatment is multimodal, encompassing systemic therapy (chemotherapy, endocrine therapy, immunotherapy, targeted therapies, etc.), surgery, and radiotherapy. However, the main therapeutic strategy for localized disease is surgical intervention[3]. Although radical and conservative surgeries have comparable survival rates, breast conservation combined with radiotherapy is the standard treatment[3,4]. Nevertheless, there are still classic indications for mastectomy: presence of previous thoracic radiation (due to previous breast cancer or Hodgkin's lymphoma), unfavorable tumor-breast relationship, extensive calcifications, multicentric disease, or in carriers of some high-penetrance genetic mutations[4].

Mastectomies that spare the skin and the nipple-areola complex (adenomastectomy) provide better aesthetic results in immediate reconstructions and are oncologically safe. Silicone implants can be positioned in the submuscular plane or in the prepectoral space[5,6].

The advantages of placing the implant in the submuscular plane are minimal visibility and palpability of the prosthesis, in addition to reduced rippling. As disadvantages, this technique can cause animation deformities, functional loss of the pectoralis major muscle, capsular contracture in varying degrees, and more postoperative pain[5,6].

The reconstruction technique with implants in the prepectoral space was initially used in the 1980s, but was promptly rejected due to high complication rates[5]. However, as of 2015, the technique aroused increasing interest, as noted in the literature, mainly in Italian centers[7].

The advent of dermal matrices has given rise to discussion regarding new possibilities for post-mastectomy reconstructions.

[1]Hospital do Câncer Aldenora Bello – São Luís (MA), Brazil.
[2]Universidade Federal do Maranhão – São Luís (MA), Brazil.
***Corresponding author:** drguara.masto@gmail.com
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Initially, they were used in a complementary way, covering the lower and lateral part, with the upper end sutured to the lower edge of the pectoralis major muscle, reducing the tension of the muscle bag. Nonetheless, this option maintained a potential risk for shoulder joint dysfunction and animation deformities associated with dissection of the pectoralis to create the muscle bag.

Aiming to remedy such damage, the prepectoral reconstruction technique with total or partial coverage of the implant by the acellular dermal matrix (ADM) has emerged. This consisted of including the prosthesis covered by the mesh in the glandular cavity itself, fixing it to the pectoralis major[5].

Although the prepectoral technique using ADM has proven to be safe and advantageous in terms of reducing complications, the use of biological meshes or synthetic materials increases its costs[8]. This fact may limit its use by paying sources, especially in the Brazilian Unified Health System (SUS) scenario. Thus, prepectoral reconstruction without coverings emerged as an alternative, showing satisfactory initial results[9,10].

This technique, however, may have disadvantages such as greater visibility and palpability of the implant, rippling, and implant extrusion. Some authors argue that undue weight and tension of the implant may put pressure on the mastectomy flap, preventing tissue perfusion[11].

Currently, there has been interest in the results of prepectoral breast reconstruction techniques and their comparison with subpectoral ones. Therefore, in this study we aim to describe the profile of patients undergoing adenomastectomy followed by immediate reconstruction technique with pre- and subpectoral implants, without the use of dermal matrix, as well as factors associated with the risk of implant extrusion.

METHODS

Study design

This is a retrospective, observational, cohort, analytical study.

Study location

High Complexity Oncology Assistance Center (*Centro de Assistência de Alta Complexidade em Oncologia* – CACON) of the state of Maranhão, Brazil, Hospital do Câncer Aldenora Bello [Aldenora Bello Cancer Hospital], maintained by the Fundação Antônio Dino [Antônio Dino Foundation], which assists patients from the Brazilian Unified Health System (SUS), health insurance plans, and private individuals.

Inclusion criteria

Women who underwent skin-sparing mastectomy or skin- and nipple-sparing mastectomy followed by immediate single-stage reconstruction with silicone implants, between January 2021 and December 2022, treated exclusively by the SUS.

Exclusion criteria

Women who underwent immediate reconstruction, using myocutaneous flaps, fat grafting, or who had an unviable area of the skin flap.

Sampling method

The sample was obtained by convenience within the proposed period, with data collection after approval by the research ethics committee, through the analysis of electronic and physical medical records, which took place from March to July 2023.

Description of surgical technique

The procedures were performed by five mastologists from this oncology reference unit, and the surgical technique was defined individually. Based on the indication profile for each technique, the sample was distributed between the prepectoral reconstruction and subpectoral reconstruction subgroups.

In the prepectoral technique, the anatomical limits were previously demarcated. The incision in the lateral third of the inframammary fold up to the muscular plane and then the dissection of the subglandular space up to signaled limits with preservation of the fascia of the pectoralis major muscle. Subsequently, the anterior glandular surface was dissected, preserving the skin flap and subcutaneous cellular tissue.

Biopsies of the retroareolar region were performed intraoperatively to rule out neoplastic involvement of the papilla. After checking hemostasis, the pocket was washed and the microtextured round silicone prosthesis was inserted, the size defined according to anatomical measurements and testing by placing molds.

Subpectoral reconstructions had different incisions according to the assessment of the attending mastologist. Some of the patients had large breasts with increased ptosis due to significant skin sagging. In these cases, a reduction mammoplasty-type incision with excision of the nipple-areola complex (NAC) was chosen, resulting in an inverted T-type scar, or a wedge incision to resect the NAC and excess skin in patients with signs of nipple-areola involvement. In the others, a periareolar or radial incision was chosen. In all cases, the gland was carefully dissected with the care already reported in the previous technique. Subsequently, the submuscular pocket was made by elevating the pectoralis major muscles and the fascia of the serratus anterior. Finally, the implant was included in this space and, subsequently, partial synthesis of the access to the pocket was performed to avoid lateral migration of the prosthesis.

In both techniques, the pocket was washed and the microtextured round silicone prosthesis was inserted, the size defined according to anatomical measurements and testing by placing molds.

Study variables

The numerical variables are: age (years), body mass index (BMI), prosthesis size (cc), breast weight (g), surgery time (minutes), and time until implant extrusion (days).

The categorical variables are: age group, BMI category, smoking habit, clinical staging (TNM), type of surgery, laterality, type of incision, histology, histologic grade, immunohistochemical profile (IHC), focality, assessment of margin involvement, type of axillary surgery, number of dissected lymph nodes, number of involved lymph nodes, contralateral breast symmetrization, adjuvant radiotherapy, neoadjuvant chemotherapy (CT), implant extrusion, and staff (anonymized by the letters A to E).

Statistical analysis

In the descriptive analysis, categorical variables are presented by frequencies and numerical variables by absolute numbers, medians, and interquartile ranges.

In the univariate analysis, Fisher's exact or Wilcoxon tests were used to associate the classification variables with the type of reconstruction technique used (prepectoral or subpectoral) and with the implant extrusion event (yes and no).

The logrank test was used to measure the difference in implant extrusion-free survival curves for each variable.

In the Cox survival model, the binary qualitative dependent variable used was the occurrence of extrusion: yes or no. The independent variables included were selected based on clinical criteria endorsed in the literature as factors associated with post-breast surgery complications.

Ethical aspects

This research was approved by the Research Ethics Committee under the CAAE (Certificate of Presentation for Ethical Consideration) consubstantiated opinion number: 69155623.9.0000.8907.

RESULTS

The study included 61 women, five of whom underwent bilateral mastectomies, one for bilateral breast cancer (synchronous tumor), and the others for risk reduction in the contralateral breast, totaling 66 mastectomies.

In Table 1 we describe the characterization of the sample stratified by surgical technique. This is a sample of young women, most of whom were over 45 years old, overweight/obese, who underwent surgery for stage II and III breast cancer, with invasive tumors of intermediate histologic grade, and a positive immunohistochemical profile of hormone receptors without overexpression of the HER-2 protein. Most tumors were unifocal, achieving free margin status at surgery. Regarding the axillary approach, sentinel lymph node biopsy (SLNB) was the most frequently performed procedure, most had up to four lymph nodes dissected and only 4.5% of the sample showed involvement of more than four lymph nodes. Most women underwent neoadjuvant chemotherapy and a smaller proportion required adjuvant radiotherapy.

In the analysis by subgroups, as shown in Table 1, the majority of patients underwent prepectoral reconstruction without the use of acellular dermal matrix (55%). Patients in this subgroup had an inframammary fold with the incision of choice and had lower values of BMI, breast weight, prosthesis size, and surgery time, with a statistically significant difference ($p<0.05$) in all these variables. The proportion of implant extrusion was similar in the prepectoral and submuscular techniques; however, we verified a tendency in the prepectoral group toward later extrusion (median of 180 days) in relation to the group with prepectoral reconstruction (median of 48.5 days), but this relationship was not statistically relevant ($p=0.066$). In the other variables analyzed, we found no statistically relevant difference between the groups.

In Table 2 we present the univariate analysis data of the sample stratified by the outcome extrusion versus no implant extrusion. We can observe that only the variables type of axillary surgery and number of involved lymph nodes showed statistical difference between the subgroups.

In Figure 1 we present the curves for implant loss-free survival analysis. Only patients with massive axillary involvement, i.e., four or more involved lymph nodes, were associated with the risk of implant loss (logrank $p<0.05$).

In Table 3 we show the Cox survival model, whose dependent variable is implant extrusion. In the model, it was possible to verify that only the degree of axillary involvement (four or more involved lymph nodes) was associated with an increased risk of implant extrusion.

DISCUSSION

Recently, skin-sparing mastectomies have been widely used worldwide for the treatment of breast cancer patients, recognized for the impact of breast reconstruction on the quality of life of female cancer survivors[5].

For decades, reconstruction with a submuscular prosthesis was considered the most viable[7-9]. The first reports of the prepectoral technique date back to the 1970s, when it was strongly associated with the occurrence of implant loss, capsular contracture, and flap necrosis[12,13]. In recent years, however, its improvement has led to new discussions on the subject, as its application has less relation to postoperative pain and there are no repercussions on the functionality of the pectoralis major muscle, in addition to the techniques having comparable complication rates[8,14-16].

In this study, acellular dermal matrix or similar material was not used to cover the implant in any of the reconstruction subgroups, considering that there is already research data that supports such practice, demonstrating that there is no increase in the complication rate, in addition to reducing costs and surgery time[8,9,16]. The implant loss rate (12%) in the general population of this study is compatible with that observed in other publications and does not present a statistically significant difference between the subgroups of each technique ($p=0.3$)[15-20].

Table 1. Epidemiological and clinical characteristics stratified by surgical reconstruction technique used.

Variables	Total n=66* (%)	Prepectoral n=36* (%)	Subpectoral n=30* (%)	p-value†
Age (years)	48 (41–53)	48 (41–54)	48 (44–52)	0.7
Age group (years)				
≤45	28 (42)	15 (42)	13 (43)	0.9
>45	38 (58)	21 (58)	17 (57)	
BMI (kg/m²)	25.8 (23.7–27.9)	24.5 (22.2–26.8)	27.0 (25.1–28.8)	**0.002**
BMI category (kg/m²)				
<25	25 (38)	19 (53)	6 (20)	**0.006**
≥25	41 (62)	17 (47)	24 (80)	
Smoking habit				
No	61 (94)	33 (92)	28 (97)	0.6
Yes	4 (6.2)	3 (8.3)	1 (3.4)	
Unknown	1	0	1	
Clinical staging (TNM)				
Stages 0 and I	18 (30)	11 (32)	7 (26)	0.6
Stages II and III	43 (70)	23 (68)	20 (74)	
NA	5	2	3	
Type of surgery				
Prophylactic	5 (7.6)	2 (5.6)	3 (10)	0.7
Therapeutic	61 (92)	34 (94)	27 (90)	
Laterality				
Right	31 (47)	17 (47)	14 (47)	>0.9
Left	35 (53)	19 (53)	16 (53)	
Type of incision				
Periareolar	14 (21)	3 (8.3)	11 (37)	**<0.001**
Radial	6 (9.1)	0 (0)	6 (20)	
Inframammary fold	33 (50)	33 (92)	0 (0)	
Inverted T	13 (20)	0 (0)	13 (43)	
Histology				
Normal breast	5 (7.6)	2 (5.6)	3 (10)	0.8
Invasive carcinoma	53 (80)	29 (81)	24 (80)	
DCIS	8 (12)	5 (14)	3 (10)	
Histologic grade				
I	15 (25)	7 (21)	8 (30)	0.5
II	33 (54)	18 (53)	15 (56)	
III	13 (21)	9 (26)	4 (15)	
NA	5	2	3	
IHC				
HR(-)/HER2(3+)	10 (16)	4 (12)	6 (22)	0.2
HR(-)/HER2(neg)	5 (8.2)	4 (12)	1 (3.7)	
HR(+)/HER2(3+)	12 (20)	9 (26)	3 (11)	
HR(+)/HER2(neg)	34 (56)	17 (50)	17 (63)	
NA	5	2	3	

Continue...

Table 1. Continuation.

Variables	Total n=66* (%)	Prepectoral n=36* (%)	Subpectoral n=30* (%)	p-value†
Focality				
Multifocal	15 (25)	9 (26)	6 (22)	0.7
Unifocal	46 (75)	25 (74)	21 (78)	
NA	5	2	3	
Margin assessment				
Free	59 (97)	32 (94)	27 (100)	0.5
Involved (superficial)	2 (3.3)	2 (5.9)	0 (0)	
NA	5	2	3	
Axillary surgery				
Not performed	7 (11)	3 (8.3)	4 (13)	0.4
SLNB	47 (71)	28 (78)	19 (63)	
Lymph node excision	12 (18)	5 (14)	7 (23)	
Number of dissected lymph nodes				
≤4	47 (71)	27 (75)	20 (67)	0.5
>4	19 (29)	9 (25)	10 (33)	
Number of involved lymph nodes				
≤4	63 (95)	35 (97)	28 (93)	0.6
>4	3 (4.5)	1 (2.8)	2 (6.7)	
Prosthesis size (cc)	418 (360–475)	380 (339–429)	440 (414–508)	**<0.001**
Breast weight (g)	352 (262–482)	276 (222–347)	499 (387–663)	**<0.001**
Surgery time (minutes)	145 (116–199)	123 (110–153)	195 (145–253)	**<0.001**
Symmetrization				
No	40 (61)	27 (75)	13 (43)	**0.009**
Yes	26 (39)	9 (25)	17 (57)	
Adjuvant radiotherapy				
No	40 (61)	22 (61)	18 (60)	>0.9
Yes	26 (39)	14 (39)	12 (40)	
Neoadjuvant CT				
No	35 (53)	18 (50)	17 (57)	0.6
Yes	31 (47)	18 (50)	13 (43)	
Implant extrusion				
Yes	8 (12)	6 (17)	2 (6.7)	0.3
No	58 (88)	30 (83)	28 (93)	
Time until extrusion (days)	146.8 (27–391)	180 (84–391)	48.5 (27–70)	**0.066**
Staff				
A	21 (32)	15 (42)	6 (20)	0.074
B	21 (32)	8 (22)	13 (43)	
C	9 (14)	7 (19)	2 (6.7)	
D	7 (11)	2 (5.6)	5 (17)	
E	8 (12)	4 (11)	4 (13)	

BMI: Body Mass Index; NA: Not applicable; DCIS: ductal carcinoma in situ; IHC: immunohistochemical profile; SLNB: sentinel lymph node biopsy; CT: chemotherapy. *Absolute numbers: interquartile range and frequencies; †Student's t-test or Mann-Whitney test; Fisher's Exact Test or χ^2 of independent samples. Bold indicates statistically significant p-values.

Table 2. Characterization of variables according to the outcome of extrusion versus no implant extrusion.

Variables	Total n=66* (%)	With extrusion n=8* (%)	No extrusion n=58* (%)	p-value†
Age (years)	48 (41–53)	51 (43–54)	48 (41–53)	0.8
Age group				
≤45	28 (42)	3 (38)	25 (43)	>0.9
>45	38 (58)	5 (63)	33 (57)	
BMI (kg/m²)	25.8 (23.7–27.9)	26.1 (24.5–27.6)	25.8 (23.5–27.9)	0.8
BMI category				
<25	25 (38)	3 (38)	22 (38)	>0.9
≥25	41 (62)	5 (63)	36 (62)	
Smoking habit				
No	61 (94)	7 (88)	54 (95)	0.4
Yes	4 (6.2)	1 (13)	3 (5.3)	
Unknown	1	0	1	
Type of surgery				
Prophylactic	5 (7.6)	0 (0)	5 (8.6)	>0.9
Therapeutic	61 (92)	8 (100)	53 (91)	
Histology				
Normal breast	5 (7.6)	0 (0)	5 (8.6)	0.6
Invasive carcinoma	53 (80)	8 (100)	45 (78)	
DCIS	8 (12)	0 (0)	8 (14)	
Histologic grade				
I	15 (25)	1 (13)	14 (26)	0.6
II	33 (54)	6 (75)	27 (51)	
III	13 (21)	1 (13)	12 (23)	
NA	5	0	5	
IHC				
HR(-)/HER2(3+)	10 (16)	2 (25)	8 (15)	0.7
HR(-)/HER2(neg)	5 (8.2)	0 (0)	5 (9.4)	
HR(+)/HER2(3+)	12 (20)	2 (25)	10 (19)	
HR(+)/HER2(neg)	34 (56)	4 (50)	30 (57)	
NA	5	0	5	
Clinical staging (TNM)				
Stages 0 and I	18 (30)	1 (13)	17 (32)	0.4
Stages II and III	43 (70)	7 (88)	36 (68)	
NA	5	0	5	
Focality				
Multifocal	15 (25)	2 (25)	13 (25)	>0.9
Unifocal	46 (75)	6 (75)	40 (75)	
NA	5	0	5	
Laterality				
Right	31 (47)	2 (25)	29 (50)	0.3
Left	35 (53)	6 (75)	29 (50)	

Continue...

Table 2. Continuation.

Variables	Total n=66* (%)	With extrusion n=8* (%)	No extrusion n=58* (%)	p-value†
Type of incision				
Periareolar	11 (17)	1 (13)	10 (17)	0.8
Radial ULQ	6 (9.1)	0 (0)	6 (10)	
Inframammary fold	36 (55)	6 (75)	30 (52)	
Inverted T	13 (20)	1 (13)	12 (21)	
Margin				
Free	59 (97)	7 (88)	52 (98)	0.2
Involved (superficial)	2 (3.3)	1 (13)	1 (1.9)	
NA	5	0	5	
Axillary surgery				
Not performed	7 (11)	0 (0)	7 (12)	0.010
SLNB	47 (71)	3 (38)	44 (76)	
Lymph node excision	12 (18)	5 (63)	7 (12)	
Number of dissected lymph nodes				
≤4	47 (71)	5 (63)	44 (76)	**0.7**
>4	19 (29)	3 (38)	16 (28)	
Number of involved lymph nodes				
≤4	63 (95)	6 (75)	57 (98)	0.037
>4	3 (4.5)	2 (25)	1 (1.7)	
Prosthesis size (cc)	418 (360–475)	465 (370–506)	410 (360–469)	0.4
Breast weight (g)	352 (262–482)	407 (243–455)	349 (262–508)	>0.9
Breast weight				
<425	43 (65)	4 (50)	39 (67)	0.4
≥425	23 (35)	4 (50)	19 (33)	
Surgery time (minutes)	145 (116–199)	160 (119–209)	145 (116–195)	0.7
Symmetrization				
No	40 (61)	6 (75)	34 (59)	0.5
Yes	26 (39)	2 (25)	24 (41)	
Adjuvant radiotherapy				
No	40 (61)	4 (50)	36 (62)	0.7
Yes	26 (39)	4 (50)	22 (38)	
Neoadjuvant chemotherapy				
No	35 (53)	2 (25)	33 (57)	0.13
Yes	31 (47)	6 (75)	25 (43)	
Technique				
Subpectoral	30 (45)	2 (25)	28 (48)	0.3
Prepectoral	36 (55)	6 (75)	30 (52)	
Staff				
A	21 (32)	3 (38)	18 (31)	0.2
B	21 (32)	1 (13)	20 (34)	
C	9 (14)	3 (38)	6 (10)	
D	7 (11)	0 (0)	7 (12)	
E	8 (12)	1 (13)	7 (12)	

BMI: Body Mass Index; DCIS: ductal carcinoma in situ; NA: Not applicable; IHC: immunohistochemical profile; ULQ: upper lateral quadrant; SLNB: sentinel lymph node biopsy.
*Median (interquartile range); †Wilcoxon test; Fisher's exact test. Bold indicates statistically significant p-values.

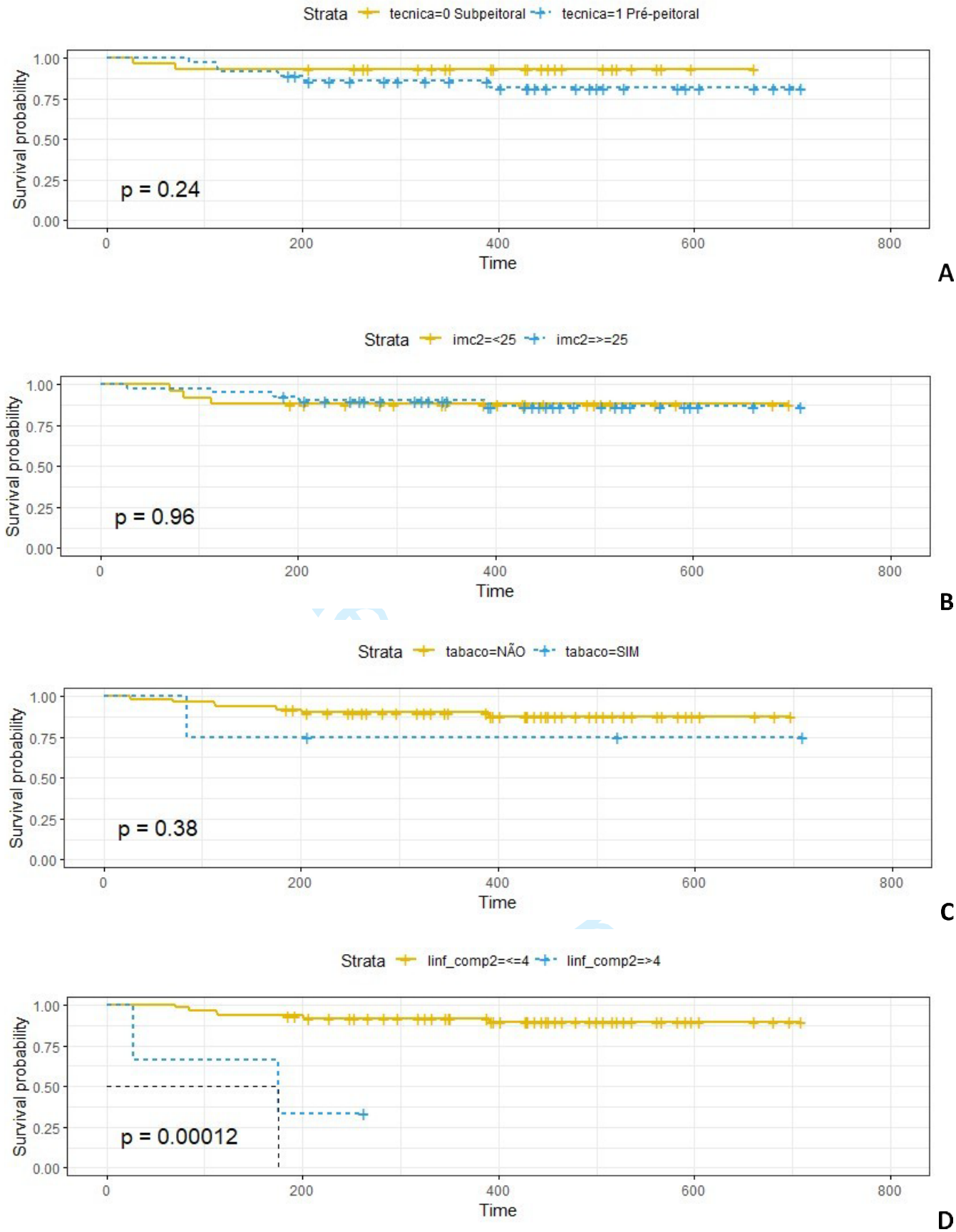

Figure 1. Implant loss-free survival. A: prepectoral technique vs. subpectoral technique; B: BMI 25; C: smoking habit yes vs. no; D: No. of involved lymph nodes ≤4 vs. >4.

Table 3. Cox survival model analysis relating time to outcome (implant extrusion) with independent variables.

Variables	No. of events	HR	95%CI	p-value	q-value*
Age group (years)	8			0.25	0.56
≤45		—	—		
>45		2.91	0.44–19.1		
BMI (kg/m²)	8			0.51	0.57
<25		—	—		
≥25		0.52	0.07–3.71		
Neoadjuvant CT	8			0.24	0.56
No		—	—		
Yes		3.60	0.38–34.0		
Adjuvant radiotherapy	8			0.40	0.57
No		—	—		
Yes		2.25	0.33–15.2		
Surgical technique	8			0.28	0.56
Subpectoral		—	—		
Prepectoral		5.19	0.20–135		
Surgery time (minutes)	8	1.00	0.99–1.02	0.48	0.57
Number of dissected lymph nodes	8			0.31	0.56
≤4		—	—		
>4		0.26	0.01–4.71		
Number of involved lymph nodes	8			**0.007**	**0.075**
≤4		—	—		
>4		76.6	2.29–2-558		
Clinical staging (TNM)	8			0.43	0.57
0-I		—	—		
II-III		2.61	0.21–32.1		
Smoking habit	8			0.090	0.49
No		—	—		
Yes		16.3	0.91–294		
Breast weight (g)	8	1.00	1.00–1.01	0.71	0.71

*False discovery rate for multiple tests.
HR: hazard ratio; CI: confidence interval; BMI: Body Mass Index; CT: chemotherapy; Bold indicates statistically significant p-values.

Among the factors linked to the demographic profile that may be associated with an increased rate of complications are high BMI (over 30 kg/m²) and breast weight[3,14,16]. In the present analysis, the general profile of the sample was similar to that of other publications and there was no statistical relevance in the comparison of patients who had or did not have extrusion (p=0.51 for BMI and p>0.71 for breast weight), similar to the results demonstrated by Hassan et al., 2021 who, despite finding a higher occurrence of implant loss in the group with higher BMI, did not demonstrate statistical significance[21].

In the comparative analysis of the subgroups, it was evident that patients who underwent subpectoral reconstruction had significantly higher BMI and breast weight, with p=0.002 and 0.001, respectively, as described by Sbitany et al.[22] The prosthesis size was also relevant in this comparison, with a larger prosthesis size in the subpectoral reconstruction group, with p<0.05. As this is a real-life, retrospective, cohort study, the selection of patients for each reconstruction technique was at the surgeon's discretion. Thus, there is selection bias between the groups, with a predominance of smaller breasts and implants in the prepectoral group. This fact was expected because this reconstruction technique is more commonly indicated for patients with smaller breasts and absent ptosis or ptosis up to grade 2[9].

Based on morphological criteria, patients with larger breasts require larger volume prosthesis for reconstruction. This fact alone has a greater relationship with the risk of flap ischemia due

to compression of the subdermal vessels[22]. Greater volume and increased ptosis are other factors that lead to an increased risk of ischemia and necrosis of the skin and NAC, therefore requiring an additional layer for protection, suggesting the indication for submuscular reconstruction[14].

The median age in the assessed population was 48 years and, in the subgroup analysis, there was no statistical difference in this regard (p=0.7). The relationship between age above or below 45 years of women with or without extrusion was also not significant (p=0.8). Advanced age is a recognized factor associated with a higher incidence of complications[23]. However, although this population demonstrated similarity with those of other studies,the relevance of this factor for extrusions was not demonstrated in these studies[21-23]. In the present research, advanced age did not represent a contraindication for reconstructions. The evaluation of indication depended on the surgeon's judgment regarding the performance status of each individual and the observation of other associated risk factors.

Smoking habit was reported by only 6.2% of patients, having low representation in this sample. The rates for this datum vary according to the time and location of the study[24]. In Brazil, the prevalence of smoking has decreased over the years[25]. Its greater association with the risk of ischemic complications and implant loss makes it a relative contraindication, which may also have impacted the decision regarding the indication for reconstruction in this population[9,14,23,26].

Prepectoral reconstructions were associated with a lower rate of contralateral symmetrization when compared to subpectoral reconstructions (25% versus 57%, p=0.009), in addition to shorter surgical time (p=0.001), as shown by Franceschini et al.[9] The correlation of shorter time of the prepectoral technique can be justified by the lack of need for dissection of the submuscular space for insertion of the prosthesis and by the lower number of contralateral breast symmetrization. In this technique, the occupation of the gland's own anatomical space by the prosthesis provided a more natural aesthetic appearance, simulating contour and ptosis similar to its previous conformation[14-16].

In subpectoral reconstructions, the least common incision was the radial one (9.1%), possibly due to its recurrent relationship with displacement of the NAC due to scar retraction that is apparent in the anterior view, leading to an unfavorable aesthetic result[20,27,28]. Periareolar incisions (37%), still highly recommended due to good access for mastectomy, axillary approach, and creation of the submuscular pocket, maintain the inconvenience of the scar in the anterior view and are losing preference[29].

In the subpectoral reconstruction population, there was a greater number of women with large breasts and, consequently, higher levels of ptosis, as such factors are related to a greater risk of complications in prepectoral reconstruction[9,14,22]. These characteristics indicate a greater possibility of the need for resection of excess skin, justifying a high rate of reduction mammoplasty-type incisions (43%) for a better aesthetic result[20,30].

Incisions through the inframammary fold were sometimes associated with greater risks due to the supposed greater tension in the suture line, as well as the possibility of venous congestion and circulatory deficit in the lower area of the flap, but in this population this datum was not relevant regarding the risk of extrusion (p=0.46)[31]. This incision was the most commonly chosen, applied in all prepectoral reconstructions, and it was not significant regarding the association with risk of extrusion (OR 2.00; 95%CI 0.29–40.2 and p=0.46), as shown in other publications[10,32]. This preference is justified by providing good access for performing the procedure, a scar in a barely visible location, and preservation of the positioning of the NAC[20,27,28].

Variables linked to complementary treatment, such as exposure to radiotherapy and chemotherapy, are known risk factors for prosthesis extrusion[3,8,21]. In this research, neither of these two factors had statistical relevance regarding extrusion, either through univariate analysis or the Cox model, results similar to recent publications[9,31,33]. The decrease in the effects of complementary therapies on implant loss rates may be related to the evolution of surgical techniques used, as well as the consolidation of knowledge of oncological safety in conservative mastectomies[5,22].

Researchers of most publications demonstrate correlations of factors linked to the individual or the treatment regarding their influence on complications or describe complication rates in a population undergoing one of the reconstruction techniques[3,34,35] As for tumor characteristics, there are few studies discussing their relevance regarding the influence on complication rates. In this context, characteristics — such as tumor type, histologic grade, immunohistochemical expression, and focality — were detailed in the present study. Invasive ductal carcinoma of no special type (IDC) was the most frequent type (61%), as described in other populations[3,31,35]. In the univariate analysis, this aspect was not statistically significant (p=0.2), corroborating Blok et al.[35]. Histologic grade, immunohistochemical expression, and focality were also irrelevant for the analyzed outcome. These results allow us to assume that tumor characteristics are in the background regarding the influence on the risk of extrusion.

Among other aspects evaluated in this analysis, the type of axillary approach has statistical relevance according to the univariate analysis, as 63% of prosthesis losses occurred in patients who underwent axillary lymph node excision (p=0.01) and in those who presented a greater number of involved lymph nodes (p=0.037). Jafferbhoy et al., demonstrated similar data, however, they did not analyze characteristics such as staging or volume of tumor involvement, variables directly linked to the indication of this type of axillary approach[6]. Within this context, women who had only neoplasia *in situ* (12%) did not have extrusion, and among those clinically staged at 0 and I, only one evolved with implant loss. Thus, when the clinical stage was related to

the outcome, more than half of the events occurred in patients classified as stage II and III. Elswick et al., reached conflicting results regarding complication rates, such as higher necrosis and dehiscence rates in the group of patients undergoing adjuvant radiotherapy, in a population in which 50% of patients were classified as stage III[34].

Another relevant aspect was the degree of axillary involvement in the histopathological analysis. In this case, there was a significance with a predominance in those who had a smaller volume of axillary disease, that is, up to four involved lymph nodes (p=0.037). However, only three women had high lymph node involvement. Therefore, these factors were included in the multivariate analysis in order to clarify discordant results.

Based on preestablished clinical criteria, variables related to a higher risk of postoperative breast complications were included in a multivariate analysis using the Cox survival model, in which a statistical correlation was observed with the degree of axillary involvement, reinforcing the assumption linked to the clinical stage. The group with greater axillary involvement (>4 lymph nodes) presented a higher risk ratio (HR 2.29; 95%CI 2.5–58). This datum indicates that axillary tumor volume may represent a risk factor for implant loss in single-stage immediate breast reconstructions. Nonetheless, individuals with this involvement profile are also included in the list of indications for chemotherapy and radiotherapy, possible confounding factors[36,37]. These aspects, despite not having demonstrated significance in this analysis, are widely correlated with the outcome according to previous analyses[31,38]. Therefore, it is necessary to include variables linked to the clinical stage and tumor volume in the final histopathological analysis, in studies with a larger population and more extrusion events.

CONCLUSIONS

Immediate reconstruction after skin- and nipple-sparing mastectomy with prepectoral implant placement without the use of cell dermal matrix was not associated with a higher risk of extrusion when compared with the submuscular technique. Large axillary involvement was the only factor associated with implant loss in this population. The study results may be limited by sample selection bias.

AUTHORS' CONTRIBUTION

PLC: Data curation, Formal analysis, Writing – original draft. YCMSR: Supervision, Validation. GMC: Supervision, Validation, Writing – review & editing. AGCO: Supervision, Validation, Writing – review & editing. RAV: Supervision, Validation. JPG: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

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ORIGINAL ARTICLE
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Temporal changes in the incidence of ductal carcinoma *in situ* in Goiânia, Brazil: a population-based study

Nayara Alves de Freitas-Lemos[1], Ruffo Freitas-Junior[1,2]*, Carleane Maciel Bandeira e Silva[3], Marise Amaral Rebouças Moreira[4], Élbio Candido de Paula[5], Nilceana Maya Aires Freitas[6], Edesio Martins[1], José Carlos de Oliveira[3], Carolina Maciel Reis Gonzaga[1], Marcus Nascimento Borges[1], Julio Roberto Macedo Bernardes Junior[7], Ricardo Francalacci Savaris[8], Régis Resende Paulinelli[1], Luiz Fernando Pádua Oliveira[1], Leonardo Ribeiro Soares[1], Rosemar Macedo Sousa Rahal[1]

ABSTRACT

Introduction: Mammography screening has resulted in a considerable increase in the diagnosis of early-stage tumors in various countries. However, most available data refer to high-income countries, hospital-based studies, or studies with limited follow-up. Therefore the aim of this study was to determine the incidence of ductal carcinoma in situ (DCIS) in Goiânia, Brazil. **Methods:** Ecological study among residents of the city of Goiânia, Brazil. We included all the DCIS cases registered at the Goiânia population-based cancer registry between 1994 and 2010. Crude incidence and age-standardized incidence rates (using the world standard population) were calculated. Poisson regression was used to analyze temporal changes, with the average annual percent change (AAPC) in the crude and age-standardized incidence rates being calculated. **Results:** There were 261 cases of DCIS, with an annual incidence rate that ranged from 0.58 to 4.21 per 1,000 women (crude and standardized) over the period. The number of cases of DCIS in the 40–49 and 60–69-years age groups increased significantly (p<0.01). The AAPC of the crude incidence rate for the period was 11.88% per year (95%CI 9–15; p<0.01) and the standardized rate was 11.89% per year (95%CI 9–15; p<0.01). **Conclusions:** The incidence of DCIS in Goiânia increased between 1994 and 2010, possibly due to improved mammography screening. The present study, which was conducted in a consolidated population-based cancer registry (PBCR) and involved an extensive follow-up time, could contribute towards increasing epidemiological knowledge on DCIS and its variations around the world.

KEYWORDS: breast carcinoma in situ; breast neoplasms; incidence; epidemiology; cesium.

INTRODUCTION

Ductal carcinoma *in situ* (DCIS) is a form of breast cancer characterized by abnormal cell proliferation confined within the basement membrane. It may present with extensive ductal involvement and lesions that render differential diagnosis difficult.[1,2] Since DCIS is considered a precursor lesion, a reduction was expected in breast cancer incidence and mortality following the advances made in the approach to DCIS over recent decades. However, even with an estimated 50,000–60,000 surgical procedures performed annually to resect DCIS, controversies remain regarding the progression of the disease and its epidemiological variations.[3,4]

The incidence of DCIS has increased expressively over recent years, perhaps as the result of the consolidation of population-based mammography screening programs and of the advances made in diagnostic methods.[2,5,6] Nevertheless, there are major

[1]Universidade Federal de Goiás, Advanced Center for Diagnosis and Treatment for Breast Cancer – Goiânia (GO), Brazil.
[2]Associação de Combate ao Câncer de Goiás, Hospital Araújo Jorge, Gynaecology and Breast Unit – Goiânia (GO), Brazil.
[3]Associação de Combate ao Câncer de Goiás, Goiânia Population-Based Cancer Registry – Goiânia (GO), Brazil.
[4]Universidade Federal de Goiás, Pathology Department – Goiânia (GO), Brazil.
[5]Association for the Combat of Cancer in Goiás, Hospital Araújo Jorge, Surgical Pathology Department – Goiânia (GO), Brazil.
[6]Association for the Combat of Cancer in Goiás, Hospital Araújo Jorge, Radiotherapy Department – Goiânia (GO), Brazil.
[7]Santa Casa de Misericórdia, Breast Department – Goiânia (GO), Brazil.
[8]Universidade Federal do Rio Grande do Sul, Surgical Sciences – Porto Alegre (RS), Brazil.
***Corresponding author:** ruffojr@terra.com.br
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differences in the rates found in different countries, with less developed countries tending to have relatively lower values. However, in less developed countries, most of the data on DCIS originate from retrospective, hospital-based studies, with incidence rates that range from 2.5 to 24.4%.[7-9] In this respect, the lack of data originating from population-based studies hampers understanding of the disease and the creation of specific public policies.[8]

Since PBCRs record incident cases of cancer in a defined population over a period of time, their use in real-world studies allows a wider exploratory data analysis to be conducted and includes the possibility of external validation. The city of Goiânia, situated in midwestern Brazil, has the longest continuously operating PBCR in the country.[10] Therefore, the objective of the present study was to determine the temporal changes in the incidence of DCIS at a PBCR in midwestern Brazil.

METHODS

An ecological study was conducted between January 1994 and December 2010 on women with DCIS. This period was chosen due to the completeness of the 10-year overall survival data, which will be reported in another study. The cases were extracted from the database of the Goiânia PBCR where data on all new cases of cancer in the municipality are collected and recorded. This PBCR was developed in 1986, and has uninterruptedly been registering all new cases of cancer in residents of the municipality of Goiânia since its creation.[10]

Cases

All cases registered as DCIS that were diagnosed in the city of Goiânia between 1994 and 2010 were included in the study. Following analysis, cases in which the women had only moved to the city after being diagnosed (untrue city residents), cases for which there was a bias in data collection (inconclusive information), and any cases in which DCIS was associated with an invasive or micro-invasive carcinoma were excluded from the study sample.[11]

Variables

The patients were divided into the following age groups: 30–39 years, 40–49 years, 50–59 years, 60-69 years and ≥70 years. Data regarding the size of the lesion (taking into consideration the largest measurement in centimeters) and nuclear grade were obtained from the surgical pathology reports. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expressions were classified as positive or negative with respect to the initial *in situ* lesion, in accordance with the description on the immunohistochemical report.

Statistical analysis

The database was created using Excel, version 2003 (Microsoft Corporation, Redmond, WA, USA). The frequency of all the variables was determined and the analysis of central tendency was performed whenever pertinent.

The crude incidence rate was defined as the ratio between the number of new cases of breast cancer *in situ* diagnosed annually and the number of women exposed to the risk of developing the disease at the midpoint of the respective year, with the result being expressed as a coefficient per 100,000 women.[12] The female population of Goiânia considered to have been exposed to the risk of cancer was calculated for each respective year based on the population census data for 1991, 2000 and 2010 and on the intercensal data for the other years.[13] The annual standardized incidence rate was calculated for each age group based on the world standard population according to Doll and Cook.[14]

The temporal changes in the incidence of DCIS were analyzed using Poisson jointpoint regression model (JoinPoint Regression, version 4.3.0, the National Cancer Institute, USA).[15] The average annual percent change (AAPC) in the crude incidence rate and in the age-standardized incidence rate was calculated. The 95% confidence intervals (95%CI) were calculated and p-values<0.05 were considered statistically significant. Statistical Package for the Social Sciences (SPSS) for Windows, version 13.0 (IBM Corp, Armonk, NY, USA) was used for the other statistical analyses.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional Ethics Committee approved the study protocol with the register number 1.940.921 (CAAE 64258216.5.0000.5078). This study fully complies with the current law of the country in which it was conducted.

RESULTS

Characterization of the sample

Between 1994 and 2010, 376 cases of carcinoma *in situ* were identified; however, 115 of these cases (44%) were excluded either because they did not comply with the classification of DCIS or due to missing data. A total of 261 cases of DCIS were included in the analysis (Figure 1).

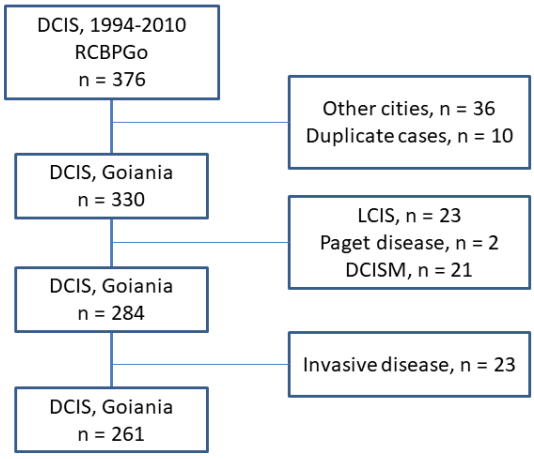
Most of the cases of DCIS registered in Goiânia occurred in women of 40 to 49 years of age (n=80), with peak registration occurring in 2009 (n=38). Tumor size was described in 51% of the surgical pathology reports, with mean size being 1.4 cm. The classification of nuclear grade was described in 68% of the reports, with 19% of the cases of DCIS being classified as grade I, 44% as grade II, and 37% as grade III. Immunohistochemical reports were available from 139 cases (49%). Of these, 56% were estrogen receptor (ER) and/or progesterone receptor (PR) positive, 26% were HER-2 positive, and 4% were triple-negative (Table 1).

Incidence

While in the 1994-2010 period 5,277 cases of invasive breast cancer were registered, with an increase from 155 cases in 1994 to 425 in 2010, there were four cases of DCIS in 1994 and 21 in 2010. For the cases of DCIS, an increase of 425% was found in relation to the first year, while cases of invasive breast cancer had an increment of 174% over the same period (Figure 2). Considering the total number of cases, the relative rate of DCIS was 4.94% (261/5,277). This increase was confirmed from the AAPC, both for DCIS and for invasive carcinomas, corresponding to 15.5 (95%CI 12.5–18.7) and 7.2 (95%CI 6.0–8.5), respectively (p<0.01).

The crude annual incidence rate of DCIS was 1.33/100,000 in 1994, and 4.21/100,000 in 2010. The incidence rate adjusted for the Doll and Cook[14] world standard population was 0.58/100,000 in 1994, and 1.85/100,000 in 2010. There was an annual increase both in the crude incidence rate of 11.93% (95%CI 9–15; p<0.01) and in the standardized rate of 11.94 (95%CI 9–15; p<0.01).

Stratifying the incidence for each 10-year age group, a significant growth was found in the number of cases of DCIS for the 40-49 years and 60-69 years age groups (p<0.01). The crude incidence rates and those standardized according to age are shown in Table 2 for 1994 and 2010 according to age groups and with the respective AAPC for each rate.



DCIS: ductal carcinoma *in situ*
RCBPGo: Registro de Câncer de Base Populacional de Goiânia
LCIS: Lobular Carcinoma *in situ*

Figure 1. Flowchart of patients included in the study.

Table 1. Characteristics of the primary tumor as retrieved from the surgical pathology and immunohistochemical reports.

Characteristics	n (%)
Age (years)*	54.21±12.30
Tumor size (cm)*	1.39±1.69
Nuclear grade	
Low (I)	31 (18.3)
High (II/III)	138 (81.7)
Total	169
Estrogen receptor	
Positive	94 (75.8)
Negative	30 (24.2)
Total	124
Progesterone receptor	
Positive	80 (66.1)
Negative	41 (33.9)
Total	121
HER2	
Positive	36 (30.8)
Negative	81 (69.2)
Total	117

*Mean±standard deviation. HER2: human epidermal growth factor receptor 2.

DISCUSSION

The incidence of DCIS has increased expressively in recent years, possibly as a result of the consolidation of population-based mammography screening programs and the advances made in diagnostic methods.[2,6,8] In Brazil, according to a telephone survey conducted with almost 268,000 individuals, mammography coverage in the country increased from 71% to 78% between 2007 and 2016.[16] Nevertheless, there is a huge difference between the rates found in different countries, with low-to-middle income countries tending to have a relatively low incidence rate compared to developed countries.[3,7-9] The present study, which was conducted in a consolidated PBCR and involved an extensive follow-up time, could contribute towards elevating epidemiological knowledge on DCIS and its variations around the world.

In the United States, according to data from the Surveillance, Epidemiology and End Results (SEER) program, the incidence of DCIS had a rapid growth following the introduction of mammography screening in the 1980s. Nevertheless, despite the stabilization

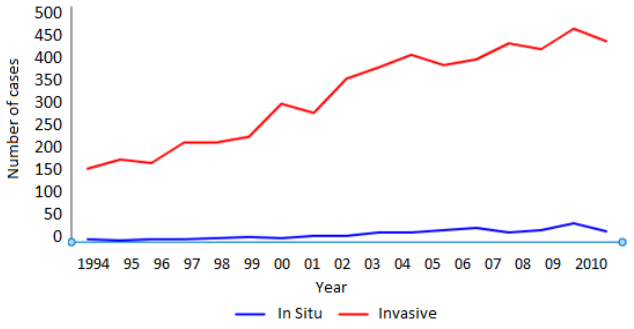


Figure 2. Evolution of the number of cases of carcinoma in situ and invasive carcinoma, in residents of Goiânia, over the years studied.

Table 2. The average annual percent change in the crude incidence rate and in the age-standardized incidence rate of ductal carcinoma *in situ* in the city of Goiânia (GO) between 1994 and 2010.

Age group (years)	Crude rate by age group*				Age-standardized incidence rate*			
	1994	2010	AAPC (95%CI)	p-value	1994	2010	AAPC (95%CI)	p-value
30–39†	1.24	1.71	-	-	0.15	0.21	-	-
40–49	1.99	5.23	6.19 (2.0–10.5)	<0.01	0.24	0.63	6.21 (2.0–10.6)	<0.01
50–59	6.06	6.36	7.46 (-0.3–15.8)	0.07	0.55	0.57	7.49 (-0.3–15.9)	0.07
60–69	0	12.40	10.35 (4.3–16.8)	<0.01	-	0.87	10.35 (4.2–16.8)	<0.01
≥70	0	12.69	10.13 (-2.5–24.4)	0.11	-	0.51	10.31 (-2.5–24.8)	0.09

AAPC: average annual percent change; 95%CI: 95% confidence interval; *Incidence rates per 100,000 women; †For the 30-39 years age group, analysis of the AAPC proved impossible since no cases were registered in some of the periods analyzed; There was only one case under 30 years of age over the entire period evaluated, making analysis of the AAPC impossible.

of screening rates over the past ten years, an AAPC of 0.8% was seen in the incidence of DCIS between 1992 and 2011.[3] In the present study, an increase of 425% was found in the standardized incidence rate of DCIS, which ranged from 0.58/100,000 in 1994 to 1.85/100,000 in 2010. Over the same period, the incidence of invasive carcinoma increased 174%. Possible explanations for this difference in proportion include the transition from analogical mammography to digital mammography and the improvement of other diagnostic methods, which could have increased the detection of early lesions.[2,3] In low-to-middle income countries, this improvement in technology occurred much later and is still occurring in some regions, explaining the elevated trend of a rise in relation to the US data for the same period.[3] Furthermore, expanded knowledge on the histology of the disease and other initiatives involving quality control in mammography could also have contributed to this increase in incidence between 1994 and 2010.[1,2,17]

The incidence of DCIS also varied according to age, race and other clinical factors. In the United States, where there is less racial miscegenation compared to the Brazilian population, a different distribution of prognostic factors was found between the racial groups analyzed, together with different incidence rates.[3,5] In the evaluation by age group, the correlation between the reduction in DCIS in women of 50-69 years of age between 2002 and 2006 and the reduction in the prescription of combined hormone replacement therapy following publication of the Women's Health Initiative (WHI) study merits particular attention.[3,18] In the same period, there was no statistically significant difference in the incidence curve in women of 40 to 49 years of age.[18] These data differ from those found in the present study, possibly due to different genetic factors or risk exposures.[19] Furthermore, the occurrence of DCIS in the over-70s (9.5%), an age group that is excluded from the majority of screening guidelines worldwide is also noteworthy.[20,21] Despite questioning on over-diagnosis and overtreatment in this population,[22] this is a very heterogenous group in which screening should be individualized in accordance with clinical status rather than chronological age alone.[23]

Considering age at diagnosis, women with DCIS also tend to be diagnosed at a younger age compared to those with an invasive carcinoma. While invasive disease is more prevalent in the 50 to 59-year age group,[9,24] DCIS appears to be more prevalent in women of 40 to 49 years of age. These data reinforce the theory that DCIS is a precursor lesion that could take up to ten years to invade the basement membrane and the breast stroma. Nevertheless, the possibility that the carcinogenesis of DCIS is different from that of invasive carcinoma and that different factors could sometimes affect the biological behavior of these pathologies cannot be ruled out.[1,2,25]

Another interesting point in the incidence of DCIS in the city of Goiânia involves the radioactive contamination accident that occurred in 1987 and the possible increase in cancer cases resulting from exposure to ionizing radiation.[26-28] Considering a latency time of 10 years, peak incidence would be expected to occur in 1997, and this was not seen. Furthermore, the incidence rate of DCIS in the city of Goiânia was found to be similar to that of the other Brazilian state capital cities where the higher incidence over time has occurred gradually.[29] These data, along with the findings of other epidemiological studies conducted in the region, suggest that there is no association between the accident involving cesium-137 and the incidence of breast cancer and DCIS.[27,28]

In recent years, in addition to the growth in the incidence rates of DCIS, a favorable change has also been seen in tumor stage at the time of diagnosis. Different studies have evaluated breast cancer staging in Brazil and, despite the inherent limitations of retrospective studies, a wide variation was found in the effectiveness of mammography screening. In the city of Barretos,[8]

which has the best organized screening system in the country, the incidence rate of DCIS was much higher than that seen in the cities of Curitiba[7] and São Paulo,[30] with rates of 16.5%, 2.9% and 8.1%, respectively. In Goiânia, the relative rate of DCIS was only 5%, which is also proportional to the poor mammography coverage (14.7%) within the public healthcare system in the mid-western region of the country.[31]

The limitations of the present study include its retrospective design and the loss of 44% of the sample due to missing or contradictory data in the Goiânia PBCR database. These limitations, however, are inherent to population-based studies,[14,32] and do not affect the credibility or the relevance of the results found. On the other hand, the strongpoints of the study were the long follow-up time and the secondary verification of the surgical pathology data that give greater robustness and innovativeness to the study.

CONCLUSIONS

The incidence of DCIS in the city of Goiânia increased between 1994 and 2010, possibly due to improved mammography screening. This increase differed as a function of the age groups analyzed and was relatively higher than the increase in the incidence of invasive carcinoma. Finally, the observed incidence was similar to the average in other regions, according to the literature.

AUTHORS' CONTRIBUTION

NAFL: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. RFJ: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review & editing. CMBS: Conceptualization, Data curation, Formal analysis, Project administration, Software, Validation, Visualization, Writing – review & editing. MARM: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – review & editing. ECP: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – review & editing. NMAF: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. EM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – review & editing. JCO: Conceptualization, Methodology, Project administration, Software, Validation, Visualization, Writing – review & editing. CMRG: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. MNB: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. JRMBJ: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. RFS: Conceptualization, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – review & editing. RRP: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. LFPO: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. LRS: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. RMSR: Conceptualization, Data curation, Methodology, Validation, Supervision, Writing – review & editing.

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ORIGINAL ARTICLE
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CDH1 methylation and expression of E-cadherin and other markers in breast cancer

Luiz Fernando de Queiroz[1], Marcelo Soares da Mota e Silva[2]*, Fernando Colonna Rosman[2], Siane Lopes Bittencourt Rosas[3], Heitor Siffert Pereira de Souza[3], Maria da Glória da Costa Carvalho[2]

ABSTRACT

Introduction: E-cadherin, encoded by the CDH1 gene, is a glycoprotein involved in cell adhesion, and the methylation of CDH1 can prevent the protein expression favoring tumor invasion. This study investigated the methylation of CDH1 in the DNA extracted from tumor and non-tumor tissues of breast cancer patients. In addition, the expression of E-cadherin, human epidermal growth factor receptor-2 (HER-2), estrogen receptor (ER), progesterone receptor (PR), and the marker of proliferation Ki-67 (Ki-67) was analyzed by immunohistochemistry. **Methods:** Samples of tumor and non-tumor breast tissues were collected from 15 women diagnosed with breast carcinoma at the time of mastectomy to analyze CDH1 methylation. The DNA was extracted, modified by the sodium bisulfite method, and amplified by polymerase chain reaction (PCR). The expression of E-cadherin, HER-2, ER, PR, and Ki-67 was evaluated by immunohistochemistry. **Results:** All the 15 patients had CDH1 methylation in the tumor tissue, and nine had CDH1 methylation in the non-tumor breast tissue. The immunohistochemical analysis showed that one patient had E-cadherin expression, three had HER-2, five had ER, six had PR, and nine had Ki-67. **Conclusions:** Our findings suggest that CDH1 gene methylation prevented E-cadherin expression in breast tumors once only one of the nine patients tested by immunohistochemical analysis showed the protein. The methylation of CDH1 in non-tumor breast tissues observed in nine patients may suggest the presence of infiltrating neoplastic cells or non-neoplastic genetically transformed cells.

KEYWORDS: cadherin-1; methylation; breast neoplasms; immunohistochemistry.

INTRODUCTION

Cadherins, a large superfamily of transmembrane glycoproteins, are integral to cell adhesion and the maintenance of tissue architecture. Among them, E-cadherin, encoded by the *CDH1* gene, is an invasion suppressor, and its dysregulation or mutation can lead to cancer development[1-3]. E-cadherin imbalance is characteristic of several malignancies and is involved in tumor metastasis[2,4]. The protein is particularly significant in the context of invasive lobular carcinoma (ILC), which accounts for 10-15% of all breast cancers[5]. The absence of E-cadherin expression is a characteristic feature of *in situ* and ILCs.

DNA methylation is a biochemical process in which a methyl group (CH_3) is added to the cytosine of a CG dinucleotide in the DNA sequence[2]. This epigenetic phenomenon can alter the gene expression without modifying the base sequence. Aberrant methylation of *CDH1* can inactivate the gene, preventing E-cadherin expression[2]. A study demonstrated the inverse relationship between *CDH1* gene methylation and E-cadherin expression in 50 cases of both ductal-type breast cancer and normal breast samples. The study showed that 94% of ductal-type breast cancers had *CDH1* promoter methylation, and that 95% of full-methylated tumor samples had no E-cadherin expression[6].

In addition to E-cadherin, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2), and the marker of proliferation Ki-67 (Ki-67) are essential markers in breast cancer. ER plays a critical role in the growth and development of breast tumors. More than 70% of breast cancers are ER positive, based on immunohistochemical analysis[7,8]. In these cases, the survival of patients can be improved

[1] Universidade Federal do Rio de Janeiro, Faculdade de Medicina, Programa de Pós-Graduação em Anatomia Patológica, Departamento de Patologia – Rio de Janeiro (RJ), Brazil.
[2]Universidade Federal do Rio de Janeiro, Faculdade de Medicina, Departamento de Patologia – Rio de Janeiro (RJ), Brazil.
[3]Universidade Federal do Rio de Janeiro, Faculdade de Medicina, Departamento de Clínica Médica – Rio de Janeiro (RJ), Brazil.
***Corresponding author:** marcelosoaresdamota@gmail.com
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by ER-positive therapy[8]. PR is a prognostic marker in breast cancer, and its high expression is more frequent in tumors with a better prognosis (luminal A) than in tumors with a worse prognosis (luminal B)[9]. HER-2 is a growth-promoting protein, and its excess or amplification of the *HER-2* gene is related to a poor prognosis of breast cancer[10]. Ki-67 is a protein associated with cell proliferation, and a high level of Ki-67 is often indicative of a more rapidly growing breast tumor[11].

This study aimed to analyze the methylation status of the *CDH1* gene in tumor and non-tumor tissues of breast carcinoma patients. Furthermore, the expression of E-cadherin, ER, PR, HER-2, and Ki-67 was examined by immunohistochemistry. We investigated whether *CDH1* methylation inhibited the expression of E-cadherin in the studied patients.

METHODS

Study design and selection of patients

This prospective hospital-based study involved 15 women treated at the *Instituto de Ginecologia* of the *Universidade Federal do Rio de Janeiro*, Brazil. The age of the patients varied between 44 and 78 years (average age: 56.7±9.6 years). All of them were diagnosed with breast carcinoma and underwent mastectomy. Before the surgery, patients were interviewed and invited to participate in the study. Those who agreed to participate were provided with all the necessary information and signed a consent form.

Data collection and ethical aspects

Patient recruitment occurred from October 2018 to July 2021. Demographic and clinical data were gathered from the patients' medical records. The study was approved by the Research Ethics Committee of the *Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro* (Certificate: CAAE #91406118.6.0000.5257, dated September 29, 2018).

Collection of tissue samples

Tumor and non-tumor surrounding tissue fragments of around 1-2 cm in each axis were collected from the breast of patients at the time of mastectomy. The tissue samples were collected at the *Instituto de Ginecologia, Universidade Federal do Rio de Janeiro*.

Extraction of DNA from tumor and non-tumor breast tissues

DNA extraction from tumor fragments and non-tumor breast tissues was performed using the phenol:chloroform method, as previously described by Mccormick et al.[12], using the UltraPure™ Phenol:Chloroform:Isoamyl Alcohol (Invitrogen, USA, Cat. No. 15593-031).

Methylation mechanism

The DNA samples were modified by the sodium bisulfite conversion method and then analyzed by the methylation-specific polymerase chain reaction (MSP) technique. DNA modification was performed using the EZ DNA Methylation-Gold™ Kit (Zymo Research, USA, Cat. No. D5005), according to the manufacturer's instructions.

Polymerase chain reaction

After the DNA modification, a fragment of exon 5 of the *P53* gene was amplified by polymerase chain reaction (PCR) to confirm the DNA integrity. The amplification reaction was performed as previously described by Pestaner et al.,[13] generating a 274-base-pair product. In the next step, the *CDH1* gene was amplified by PCR. For the *CDH1* amplification, two pairs of primers were used as follows: *CDH1*-U (unmethylated) forward, 5′-GGTAGGTGAATTTTAGTTAATTAGTGGTA-3′ and *CDH1*-U reverse, 5′-ACCCATAACTAACCAAAAACACCA-3′, producing a fragment of 211 base pairs, and *CDH1*-M (methylated) forward, 5′-GGTGAATTTTAGTTAATTAGCGGTAC-3′ and *CDH1*-M reverse, 5′-CATAACTAACCGAAAACGCCG-3′, producing a fragment of 204 base pairs[14]. The polymerase used was the GoTaq G2 Hot Start Green Master Mix (Promega, USA, Cat. No. M7422). The cycling included an initial denaturation at 96°C for 7 min, followed by 35 cycles of 95°C for 1 min, 62°C for 1 min, 72°C for 1 min, and a final extension at 72°C for 5 min.

Gel electrophoresis and staining

The PCR products were run by electrophoresis in 10% polyacrylamide gel. A negative control and a DNA marker were included in each electrophoretic run. Gels were stained by the silver nitrate method involving DNA fixation with ethanol and acetic acid, impregnation with silver nitrate, and revelation of the DNA bands with sodium hydroxide (NaOH) and formaldehyde[15].

Histopathological and immunohistochemical analysis

The tissue samples were fixed in 10% formalin and embedded in paraffin wax. The tissue blocks were sectioned into 4 μm thickness sections. The hematoxylin-eosin staining was used for the histopathological analysis. The immunohistochemistry was accomplished with monoclonal antibodies for all antigens. The primary antibodies used were rabbit anti-E-cadherin (clone EP700Y, 1:200, Cell Marque), mouse anti-HER-2 (clone CB11, 1:600, Cell Marque), rabbit anti-ER (clone SP1, 1:200, Cell Marque), mouse anti-PR (clone 16, 1:100, Cell Marque), and rabbit anti-Ki-67 (clone SP6, 1:300, Spring). The secondary antibody applied was from the Novolink Polymer Detection System® (Leica Biosystems, UK, product code: RE7280-K), following the manufacturer's instructions.

RESULTS

Table 1 shows the methylation panel of the *CDH1* gene in the tumor and non-tumor breast tissues. All the 15 patients had *CDH1* methylation in the tumor tissue. Nine patients had *CDH1* methylation in the non-tumor breast tissue.

Out of the 15 patients, samples from nine patients were analyzed by histopathology and immunohistochemistry. As indicated in Table 2, E-cadherin expression was detected only in patient five. All the nine patients tested positive for Ki-67. As determined through the immunohistochemical analysis, the classification of tumor subtypes was as follows: luminal A (patients 2, 7, and 8), luminal B (patients 6 and 10), HER-2-positive (patient 5), and triple-negative (patients 3, 4, and 14). The histopathological grades and types of breast carcinomas are described in Table 3.

Table 4 shows the age and TNM stage of the patients. It is noteworthy that all patients with this information available fell within a tumor category of 3 or 4, representing an advanced disease. Photomicrographs of the histological sections of tumors are displayed in Figures 1 and 2.

Table 1. Methylation panel of the cadherin 1 (*CDH1*) gene in tumor and non-tumor breast tissues.

Patient number	Tumor breast tissue	Non-tumor breast tissue
1	M	U
2	M	M
3	M	U
4	M	M
5	M	U
6	M	M
7	M	M
8	M	U
9	M	M
10	M	M
11	M	U
12	M	M
13	M	M
14	M	M
15	M	U

M: *CDH1* methylated. U: *CDH1* non-methylated.

DISCUSSION

Our study investigated the methylation status of the *CDH1* gene in tumor and non-tumor tissues of breast cancer patients. Additionally, we analyzed the expression of E-cadherin, ER, PR, HER-2, and Ki-67 by immunohistochemistry.

The results showed that *CDH1* gene methylation was detected in the tumor of all the 15 patients and in the non-tumor breast tissue of nine patients (Table 1). Otherwise, only patient number five presented E-cadherin protein expression in the immunohistochemical analysis, suggesting that *CDH1* methylation prevented E-cadherin expression in the other patients. This aligns with the findings of Shargh et al.[6], who reported that, in a group of 50 breast cancer patients, 94% had *CDH1* methylation and 95% of full-methylated tumor samples had no E-cadherin expression. In another study, Corso et al. emphasized that the detection of *CDH1* epigenetic alterations in a diagnostic/pre-operative biopsy may be helpful to improve patient management and to infer the prognosis of breast cancer and the pattern of tumor dissemination[16].

Table 2. Invasive ductal and invasive lobular carcinoma: Immunohistochemical analysis reports.

Patient number	Invasive Ductal Breast Carcinoma – Patients 2, 3, 4, 7, 8, 10, and 14 Papillary intraductal carcinoma – Patient 6 ILCs – Patients 5 and 6				
	ER Positive (%)	PR Positive (%)	Ki-67 Positive (%)	HER-2 Positive (%)	E-cadherin Positive (%)
2	100	100	1–5	0	0
3	0	0	80-90	0	0
4	0	0	80-90	0	0
5	Not available	20–30	20–30	Score 3 (>30%)	Positive
6	100	90–95 (infiltrating) 20–30 (intraductal)	30–40	0	0
7	60–70	10–20	5–10	0	0
8	100	100	5–10	0	0
10	100	90–95	50-60	Score 1 (≤10%)	0
14	0	0	80-90	Score 1 (≤10%)	0

ER: estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor receptor-2; Ki-67: marker of proliferation Ki-67; ILCs: invasive lobular carcinomas.

Table 3. Histopathological analysis reports (breast carcinoma types).

Patient number	Ductal infiltrating carcinoma, non special type	Ductal carcinoma *in situ*	Ductal carcinoma *in situ* Grade 1 without comedonecrosis	Ductal carcinoma *in situ* Grade 2 with comedonecrosis	Intraductal papillary carcinoma	ILC
2	Grade 2	Grade 1	P	-	-	-
3	P	-	-	-	-	-
4	Grade 3	-	-	-	-	-
5	-	-	-	-	-	P
6	-	-	-	-	P	P
7	Grade 1	-	-	-	-	-
8	Grade 1	Grades 1 and 2	P	-	-	-
10	Grade 2	Grade 2	-	P	P	-
14	Grade 3	-	-	-	-	-

P: positive for the types of carcinomas of the study patients. Grade 1: well differentiated. Grade 2: moderately differentiated. Grade 3: poorly differentiated. ILC: invasive lobular carcinoma.

Table 4. Age and TNM stage of patients.

Patient number	Age (years)	TNM stage
1	53	T4b N2 Mx
2	73	WD
3	50	WD
4	44	T3 N0 M0
5	49	CT3 CN2 CM0
6	59	T4 N0 Mx
7	44	T4B N1 Mx
8	49	T3 N1 Mx
9	78	WD
10	57	T4 N0 Mx
11	57	T4 N1 Mx
12	56	T4B N0
13	59	T3 N1 M0
14	54	T4b N2 Mx
15	69	T3 N0 M0

TNM acronym refers to TNM Classification of Malignant Tumors, where "T" refers to primary tumors, "N" refers to nearby lymph node involvement, and "M" refers to distant metastasis. WD: TNM stage not described in the records.

Three patients (2, 7, and 8) were diagnosed with luminal A subtype carcinoma, characterized by a strong positivity for ER and PR, a negativity for HER-2, and a weak positivity for Ki-67 (Table 2). As pointed out by De Santo et al.[17], the luminal A subtype is associated with less biologically aggressive neoplasms and is responsive to anti-estrogenic therapy. However, over time, neoplastic cells can develop resistance to this therapy due to mutations in the genes of ERs. This resistance can interfere with the action of anti-estrogen drugs, such as tamoxifen, thereby favoring cancer progression.

Three patients (3, 4, and 14) were diagnosed with the triple-negative subtype, characterized by a high Ki-67+ (80-90%) due to the elevated degree of the proliferation of neoplastic cells. This subtype presents an aggressive clinical behavior, as pointed out by Derakhshan and Reis-Filho[18]. Furthermore, the triple-negative subtype is associated with neoplasms of high combined histopathological grade, which agrees with our findings reported in Table 3 (patients 4 and 14 had Grade 3). This characteristic favors response to neoadjuvant chemotherapy.

Patient number five, diagnosed with ILC, was HER-2+. This patient showed *CDH1* methylation and E-cadherin expression only in the tumor and not in the non-tumor tissue, confirming the heterogeneity of E-cadherin expression in lobular carcinomas[5].

The histopathological diagnosis summarized in Table 3 allowed an initial prognostic assessment. Histopathological analysis is indispensable to direct complementary molecular studies (including immunohistochemistry and methylation analysis). These studies are essential to improve diagnosis and assist in choosing the most appropriate treatments, allowing a better evaluation of the final prognosis in patient survival.

TNM stage information was available for 12 out of the 15 patients (Table 4). All of them had advanced tumors (seven had T4 and five had T3), which is related to late diagnosis, delay in treatment start, and reduced survival, as emphasized by Rivera-Franco and Leon-Rodriguez[19].

To our knowledge, this is the first study that simultaneously explored *CDH1* gene methylation and E-cadherin protein expression in a cohort of Brazilian breast cancer patients.

CONCLUSIONS

Our findings suggest that *CDH1* gene methylation prevented E-cadherin expression in breast tumors once only one of the nine patients tested by immunohistochemical analysis showed the protein. The methylation of *CDH1* in non-tumor breast tissues observed in nine patients may suggest the presence of

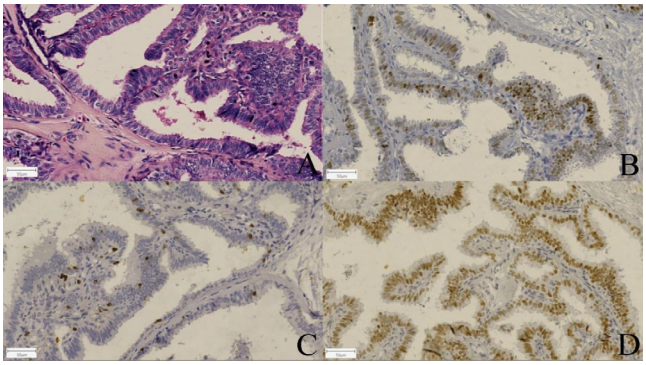

Figure 1. Histological sections of papillary carcinomas. The scales correspond to 50 µm in length. HE: hematoxylin-eosin staining. A: Intraductal papillary carcinoma, HE. B: Intraductal papillary carcinoma with nuclear PR positivity, IH. C: Intraductal papillary carcinoma with nuclear Ki-67 positivity, IH. D: Intraductal papillary carcinoma with nuclear ER positivity, IH.

IH: immunohistochemistry. PR: progesterone receptor. Ki-67: marker of proliferation Ki-67. ER: estrogen receptor.

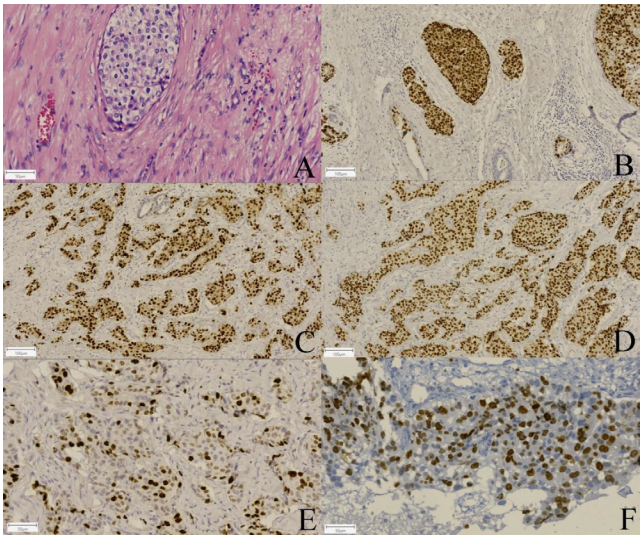

Figure 2. Histological sections of ductal carcinomas. A: in situ ductal carcinoma, HE. B: in situ ductal carcinoma with nuclear PR positivity, IH. C: invasive ductal carcinoma with nuclear PR positivity, IH. D: invasive ductal carcinoma with nuclear ER positivity, IH. E: invasive ductal carcinoma with nuclear Ki-67 positivity, IH. F: invasive ductal carcinoma with nuclear Ki-67 positivity, IH. In A, E, and F, the scales correspond to 50 µm in length. In B, C, and D, the scales correspond to 100 µm in length.

HE: hematoxylin-eosin staining, IH: immunohistochemistry. PR: progesterone receptor. Ki-67: marker of proliferation Ki-67. ER: estrogen receptor.

infiltrating neoplastic cells or non-neoplastic genetically transformed cells. New studies are needed to analyze the methylation of other genes that encode markers for breast cancer, such as ER, PR, HER-2, and Ki-67. Furthermore, these studies should investigate the relationship between gene methylation and the respective marker expression.

AUTHORS' CONTRIBUTION

LFQ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. MSMS: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. FCR: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. SBLR: Formal analysis, Investigation, Methodology, Writing – review & editing. HSPS: Funding acquisition, Resources, Writing – review & editing. MGCC: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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REVIEW ARTICLE
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Association between obesity and triple-negative breast cancer: a systematic qualitative review

Luiz Lerario Iervolino[1], Sérgio Rodrigues de Moraes[1]*, José Roberto Filassi[1], Edmund Baracat[1], Sérgio Masili-Oku[2]

ABSTRACT

Introduction: The relation between obesity and triple-negative breast cancer (TNBC) is not totally elucidated. TNBC represents a heterogeneous group of aggressive growth neoplasms. The concepts related to the development of hormone receptor-positive tumors cannot be directly extended to this group. To evaluate the association between obesity and TNBC, considering as primary outcome the assessment of the incidence of this tumor subtype in this population and as secondary outcomes the specific pathophysiology, prognosis, and treatment in this context. Methods: This was a systematic review following the Preferred Reporting Items for Systematic reviews and Meta-Analyses — PRISMA statement. PubMed/MEDLINE and Cochrane were the databases used as primary paper sources. Inclusion according to titles and abstracts allowed a secondary selection by reference list revision. The final full-text review was done on the most opportune studies identified. Results: A total of 52 articles were included. Epidemiology: A higher frequency of obesity among TNBC patients compared to other subtypes and TNBC in obese women was observed in the literature. It is uncertain whether premenopausal status is an aggravating factor. Pathophysiology: Several studies identified the production of different factors by obese adipose tissue and their regulation of genes related to the expression of stem-like cell properties, mainly leptin, IL-6, and IL-8. Prognosis: Most studies pointed out that disease-free survival and overall survival are independent of body mass index. Treatment: Weight reduction showed no significant power in improving prognosis but may favor primary incidence prevention. Drugs based on obesity-related pathways are still in research, and various potential targets were raised. Conclusions: Obesity is a risk factor for TNBC. Obese-related inflammatory cytokines may contribute to tumor development. Once TNBC is established, the prognosis does not differ according to initial body mass index changes. No target drug for obesity-related tumorigenic pathways is currently available for clinical use.

KEYWORDS: obesity; breast neoplasm; triple negative breast cancer.

INTRODUCTION

The relationship between obesity and breast cancer is an old topic of discussion and investigation. Over years of epidemiological research and observation, it has become clear that the interaction of body mass index (BMI) with breast tumorigenesis could not be simplified into one unique conclusion. This binomial showed itself to be complex and heterogeneous. Different associations were found depending on multiple context factors such as ethnicity, menstrual status, and anatomopathological tumor type.

The well-established association is obesity in postmenopausal women as a risk factor for hormone receptor-positive breast cancer. Pathophysiology justifying this influence was initially well-understood and supposedly simple. The higher and maintained estrogenic synthesis, by aromatase enzyme conversion of adrenal androgens in adipose tissue, could stimulate the breast cells proliferation that expressed those hormone receptors[1]. However, past decade data already point to other factors synthesized by adipose tissue that could have a synergistic carcinogenic effect on the breast and other organs, as well.

The connection between triple-negative breast cancer (TNBC) and obesity is not entirely intuitive. TNBC consists of the most aggressive subtype and stands for 20% of breast cancer cases. The absence of hormone or HER2 expression reflects the difficulty to treat the cancer, as no targeted therapy has been developed to date[2].

[1]Universidade de São Paulo, Hospital das Clínicas – São Paulo (SP), Brazil.
[2]Instituto do Cancer Doutor Arnaldo Vieira de Carvalho – São Paulo (SP), Brazil.
***Corresponding author:** moraes.sergio.13@gmail.com
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Recently, numerous lines of research have been interested in this subtype of tumor. Pro-inflammatory activity related to adipose tissue has brought to light more consistent data concerning the possibility of obesity as a risk factor for TNBC development.

This systematic review aimed to concentrate on and explore the prior global knowledge already published in the scientific literature about the association between obesity and TNBC.

As a primary outcome, we intended to evaluate whether the incidence of TNBC is proportionally higher in the obese population. As secondary outcomes, we evaluated the pathophysiology that could explain such an association, the prognostic effect of obesity in a patient with this tumor subtype, and the targeted treatments that could be applied in this specific associative context.

The data presented in this article were designed to concisely report to generalists and specialists what is known about this issue so that they can improve their practice based on available evidence.

METHODS

This review was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[3] (Figure 1). A systematic search was conducted to determine relevant articles published until July 1, 2022, using two primary biomedical literature databases: PubMed/MEDLINE and Cochrane. The following terms were used to access papers of interest broadly: ((triple-negative breast cancer) OR (basal-like)) AND ((BMI) OR (obesity)). No limits were placed on the country or publication date. All types of studies, descriptives or analytics were accepted. Studies in process or only published in conference annals were not included.

Only articles in English were selected. Studies in which TNBC was analyzed, among other types of breast tumor, were also considered. Studies with women across both premenopausal and postmenopausal status were considered for analysis. Animal model studies were also included. After the initial exclusion of duplicates, titles and abstracts were revised, allowing the first filtration of our bibliography, selecting the articles with probably the highest impact for the full-text review.

A secondary selection of opportune papers for analysis was performed. Additional studies were identified by reviewing the reference lists of the first listed studies that met the inclusion criteria.

After full-text evaluations, the last refinement was concluded, finishing the selection process of adequate literature for this topic review. This systematic review was performed from this condensed but relevant group of articles. Thereafter, the study's samples, methods, results, and conclusions were qualitatively described. No statistical analysis was conducted on these data.

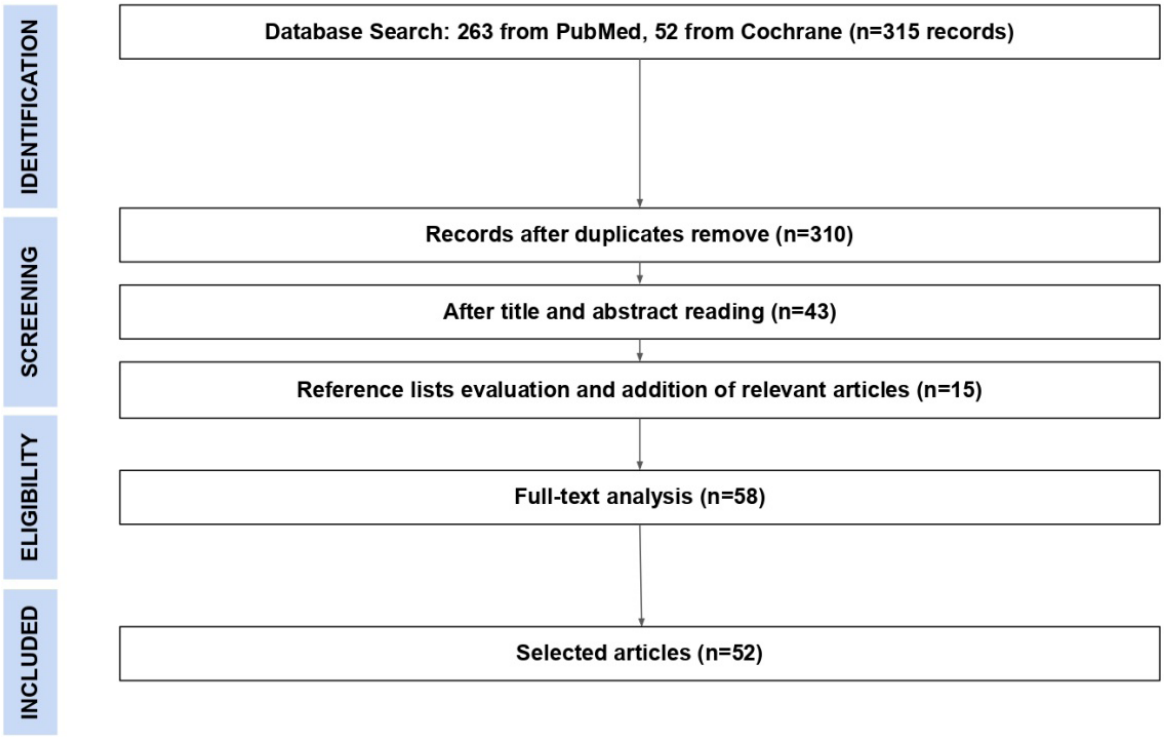

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for systematic review articles selection.

This article's discussion of the relationship between obesity and TNBC was carefully and objectively detailed based on the most consistent data available. Aiming for a straightforward approach, we organized epidemiology, pathophysiology, prognosis, and interventions.

RESULTS

The primary literature search yielded 310 articles, considering 263 from PubMed, 52 from Cochrane, and the removal of five duplicates. After the title and abstract reading, 43 studies directly related to the association between obesity and TNBC were selected. We added 15 other opportune studies by their reference lists evaluation, reaching 58 articles for full-text analyses. After reading all 58 texts, we ended up with 52 primary studies covering epidemiology, pathophysiology, prognosis, and treatment subtopics.

Epidemiology

There are multiple studies concerning TNBC patients' characteristics. However, the pathophysiology of this tumor subtype has not been elucidated yet. Therefore, populational analyses have always been a first step in bringing to light this disease mechanism.

Through extensive sample studies, including initially its different subtypes, breast cancer incidence showed itself to be directly related to obesity frequency, and over years of detailed research comparing individual characteristics between breast cancer subtypes, TNBC alone also presented a frequent association with obesity in concordance with general tendency.

Millikan et al. found an increasing waist-hip ratio positively associated with basal-like tumors, even though no relation was observed with BMI[4]. After that, several studies pointed to a higher frequency of obesity among TNBC patients compared to other subtypes or obesity as a significant risk factor for TNBC[5-12]. Somali et al., Enger et al., and Maiti et al., found no relationship between obesity and TNBC[13-15].

Pierobon's meta-analysis with 3,845 patients diagnosed with TNBC, which evaluated breast cancer, obesity, and menopausal status, concluded that this association between obesity and TNBC was only valid for women with premenopausal status[10]. This corroborated a previous study by Gaudet, which comprised women under 56 years old and restricted its conclusion of TNBC increased risk by obesity only to premenopausal status[9]. Also, in a pooled analysis of 34 studies comprising 35,568 patients, of which 1,997 had TNBC, Yang et al. identified an association between obesity and breast cancer confined to TNBC cases in women younger than 50 years old[8]. An epidemiological difference was then established with the protective effect obesity imposes over hormone receptor-positive tumors in premenopausal women[11].

Concerning racial differences in this context, Siddharth et al. suggested a higher frequency of obesity among African-American women compared to European-American ones as one of the factors that could explain the TNBC earlier onset and more advanced stage at diagnosis in that population. Other factors related would be a genetic risk, low income, and inadequate screening[16].

In Table 1, we listed and summarized the main epidemiological studies that evaluated the association between TNBC and obesity. It is observed that the correlation is positive in the majority of the studies (8 out of 11), with a particular emphasis on the premenopausal period.

Pathophysiology

Obesity has already been linked to the development of different types of cancer. Concerning TNBC, a couple of articles examined molecular factors and pathways that may favor this tumor's emergence in obese patients, as summarized in Figure 2. Most of these studies are ***in vivo*** research using TNBC cells inoculated in animal models.

The main primary changes in an obese organism described as possible triggers for TNBC tumorigenesis are adipose tissue mechanical stress and hypoxia, with adipocyte death and consequent systemic inflammation. A second pathway recurrently explored is the high leptin levels observed in obese individuals, being directly associated with TNBC severity[15,17,18].

Adipose tissue is responsible for inflammatory cytokines release, including IL-6, IL-8, IL-12, CCL2, and IL-1β[19]. Leptin and IL-6 are related to increased macrophage migration to adipose tissue and their subtype change from type 1 to type 2. Type 2 macrophages secrete IL-6 (dependent on NADPH oxidase 2 activity), IL-8, TGF-β, and EGF. Also, leptin stimulates T cell release of IL-2 and IFN-γ[20,21].

Leptin, IL-2, and IFN-γ from T cells, IL-6, and TNF-α (through glycoprotein 130) from type 2 macrophages can activate STAT3/JAK2, NF-κB, and Wnt/EZH2[17,20,21]. These transcription factors regulate the expression of NANOG, SOX2, and OCT4 — genes that are shown to induce stem-like properties in TNBC cells, including renewal capacity[18,21].

In addition, obese individuals present low natural killer (NK) cell number and activity that have already been associated with poor prognosis in TNBC[22]. NK cells play a role against tumor cells' survival, and chronically elevated leptin levels can decrease leptin receptor sensibility, resulting in the downregulation of cytotoxic activity[23]. Naik et al. described this immune pathway by which obesity could favor TNBC progression[24].

Teslow et al. reported that inflammation and reactive oxygen species derived from the obesity context can regulate splicing factor serine/arginine-rich splicing factor 2 (SRSF2), which augments the expression of methyl-CpG-binding domain variant 2 (MBD2-v2) that is another inductor of NANOG overexpression[25]. Additionally, Kolb et al. presented that inflammation enhances the

Table 1. Previous articles that evaluated the association of triple-negative breast cancer incidence with obesity.

Studies	Country	Sample size	Study design	Main findings	Odds ratio or p-value	Risk of bias
Enger et al.[14]	U.S.A.	1,184 cases; 272 TNBC	Case-control (two groups: pre and postmenopause)	Body mass index was not associated with TNBC, including BMI>27	No association was found regarding BMI	Low cut point regarding BMI>27
Milikan et al.[4]	U.S.A.	1,424 cases; 225 basal-like	Case-control	Elevated WHR was associated with increased risk of basal-like breast cancer in pre and postmenopausal women compared to luminal A cases and controls.	WHR 0.77–0.83: OR 2.3 (95%CI 1.5–3.5)/≥0.84: OR 2.3 (95%CI 1.4–3.6) (referent to controls)	Higher incidence of basal-like tumors among African-Americans
Vona-Davis et al.[5]	U.S.A.	620 cases; 117 TNBC	Retrospective cohort	Obesity was present in 49.6% of those with triple-negative tumors but in only 35.8% of those with non-triple-negative tumors.	p=0.0098	No analysis according to age subgroups
Kwan et al.[7]	U.S.A.	2,544 cases; 288 TNBC	Prospective cohort	Compared with luminal A cases, triple-negative cases tended more likely to be overweight or obese if premenopausal	Overweight: OR 1.82 (95%CI 1.03–3.24)/Obese: OR 1.97 (95%CI 1.03–3.77)	Higher incidence of TNBC among African-Americans
Maiti et al.[15]	U.S.A.	176 cases; 86 TNBC	Retrospective cohort	Triple-negative breast cancer is associated with a higher prevalence of the metabolic syndrome but not with higher BMI	No association was found regarding BMI	Reduced population, retrospective study
Trivers et al.[6]	U.S.A.	476 cases, 135 TNBC	Case-control	Women with TN tumors were more likely to be obese than normal/ underweight	OR 1.89 (95%CI 1.22–2.92)	Tumor specimens were available only on a subset of eligible cases
Yang et al.[8]	U.S.A.	35,568 cases; 1,997 TNBC	Pooled analysis 34 studies/Case control	Association in women <50 years between obesity and breast cancer confined to TNBC cases	OR 1.80 (95%CI 1.42–2.29)/ p=0.000002	Differences in study populations, designs and methods of collecting risk factors, and marker data
Gaudet et al.[9]	U.S.A.	890 cases; 246 TNBC	Case-control	Larger body size among premenopausal women was associated with higher risk of luminal B and TNBC	OR 1.67 (95%CI 1.22–2.28)/p=0,026 (compared to luminal A)	Biased observed findings for unmeasured risk factors, staining obtained by a single pathologist
Pierobon et al.[10]		24,479 cases; 3,845 TNBC	Systematic review and meta-analysis	The case-case and case-control comparisons showed a significant association between TNBC and obesity	Case-case: OR 1.2 (95%CI 1.03–1.4)/ p=0.003 Case-control: OR 1.43 (95%CI 1.23–1.65)/p=0.913	

Continue...

Table 1. Continuation.

Studies	Country	Sample size	Study design	Main findings	Odds ratio or p-value	Risk of bias
Somali et al.[13]	Turkey	882 cases; 132 TNBC	Retrospective cohort	No significant difference was observed in terms of BMI between postmenopausal and premenopausal patients in the TNBC group	p=0.08	Patients with unknown menopausal status, >50 years old were considered postmenopausal
Chen et al.[11]	U.S.A.	2,659 cases; 1,275 TNBC	Case-case-control	Obese premenopausal women had an increased risk of TNBC while obese postmenopausal women had a reduced risk of TNBC	Pre: OR 1.82 (95%CI 1.32–2.51)/ p=0.004 Post: OR 0.74 (95%CI 0.54–1)/ p=0.032	Case-case comparison should not be extended to a cancer-free population

U.S.A.: United States of America; TNBC: triple-negative breast cancer; BMI: body mass index; CI: confidence interval; WHR: waist-hip ratio; OR: odds ratio.

upregulation of angiopoietin-like 4 (ANGPTL4) in adipocytes. This condition leads to angiogenesis and progression of breast cancer[19].

High levels of leptin and leptin receptor activity have also been shown to promote Serpine-1 gene expression that codifies serine protease inhibitors in vascular epithelial cells. Through binding vitronectin, this protein favors the detachment of cancer cells, facilitating metastasis. Leptin knockdown resulted in a diminution of metastasis[26].

A third pathway described by which obesity could be associated with TNBC development is chronic hyperglycemia. D'Esposito et al. showed that TNBC cells become more invasive when cultivated with adipocytes and even more when exposed to a hyperglycemic environment. Hyperglycemia increases CCL5 produced by adipocytes that bind to CCR5, which activates STAT3/JAK2, mTOR, and p38MAP kinase. CCL5 presence in adipose tissue was associated with lymph node positivity and metastasis[27]. In concordance, Dietze et al. showed that hyperglycemia through induced hyperinsulinemia and IGF-1 raise could activate AKT/mTOR cascade, resulting in elevated glucose uptake by the cell ending on the Warburg effect[20].

Prognosis

Previously, it has already been shown that obesity appears to be a factor in poor prognosis for breast cancer in general. Ewertz et al., in a large sample Danish study with 18,967 patients, revealed an increase in metastasis and death frequency in obese patients with breast cancer compared to non-obese ones; however, cancer subtypes were not discriminated[28].

Despite a general investigation of obesity and breast cancer development, researchers have been specifically interested in evaluating the influence of obesity according to each cancer subtype. In the last decade, a couple of studies were dedicated to analyzing if obesity could or could not be confirmed as a possible factor for a poor prognosis in TNBC. The results found were not always homogeneous.

In a systematic review and meta-analysis including nine studies comprising 4,412 TNBC patients, Mei et al. concluded that disease-free survival (DFS) and overall survival (OS) were independent of BMI[29]. This was consistent with other studies not included in this meta-analysis[30-34]. It is valid to point out that Dawood et al. and Tait et al. analyzed their sample by menopausal status and still found no significant influence of BMI over TNBC prognosis between pre and postmenopausal groups[31,33]. Schmidt et al., however, presented similar results but with a 70% postmenopausal sample[34]. Also, Mowad et al., despite finding larger tumor size and grade staging, DFS and OS remained indifferent among obese and non-obese individuals[32].

In counterpoint, some authors found a positive association between obesity and TNBC's poor prognosis, including DFS and OS. Through these studies, attention should be taken to Turkoz et al. presenting an all-premenopausal sample and Loi et al. a 74% one[35,36]. Also, Hao et al., Bao et al., and Al Jarroudi et al. found a worse prognosis exclusively among the premenopausal group[37-39]. However, Choi et al. described no difference according to menopausal status, comprising only 50 patients[40]. Chen et al., independent of menopausal status, similarly presented a decrease in DFS and OS in the obese group and were the first, to our knowledge, to include in the analyses the abdominal circumference, not only the weight, finding a worse prognosis in the group with both general obesity associated with central obesity[41].

Additionally, Maehle et al. described a better prognosis for their obese negative hormone receptor group than the non-obese one, considering that the sample was 75% composed of postmenopausal women and TNBC individuals were not isolated[42].

Treatment

Since there is no available well-established target therapy for TNBC, modifiable risk factors, such as weight intervention, have been a source of interest in the last years for prevention or even cancer progression impairment.

Eliassen et al., in a large prospective cohort study within the Nurses' Health Study, including 87,143 postmenopausal patients followed up for 24 years, observed an increased risk for general breast cancer associated with weight gain since the age of 18

years. This pointed to weight maintenance or loss as a possible prevention method. However, TNBC was not evaluated separately[43].

Enger et al. precisely found a tendency of risk increase of breast cancer by weight gain during the menace restricted to hormone receptor-positive tumors. Hormone receptor-negative tumor risk was independent of weight change, and physical activity frequency was also evaluated. Weight loss or physical activity after diagnosis was not evaluated[14].

First, *in vivo* studies showed reverse TNBC progression and delayed tumor latency in obese mice submitted to weight loss on a low-fat diet. This phenomenon was associated with a reduction in kinases (PKC-α, PKD1, PKA, and MEK3) and an increase in AMPKα activity[44,45].

However, studies with TNBC patients did not show that clear correlation. In a 518 Chinese patients study, weight loss was associated with higher tumor recurrence and mortality than stable weight[38]. In a second study with 173 patients, weight change — gain or loss — did not correlate with Ki67 or pathologic complete response change during neoadjuvant chemotherapy[46]. In counterpoint, Wang et al. described JAK/STAT3-regulated fatty acid β-oxidation as critical for cancer stem cell self-renewal and chemoresistance, which could be more evident in obese patients[47].

Finally, some authors tested therapeutic drug alternatives for TNBC related to obesity pathophysiology. Otvos et al., in a mouse xenograft model for TNBC, found a significant average survival increase by subcutaneous Allo-aca (a leptin receptor antagonist) administration compared to conventional intraperitoneal cisplatin[48]. Similarly, Gourgue et al. described a reduction in TNBC growth with apelin antagonist F13A. This substance reduces apelin activity, an adipokine increased in adipose tissue of obese mouse tumors[49].

Naik et al., in an extensive discussion about immune pathways related to TNBC development and progression in obese organisms, suggested some hypothetical points of possible therapeutic interventions to be studied:

1) PD-1/PD-L1 suppression, since in a study with 250 patients, obese ones got the major benefit of this intervention than lean individuals. Being PD-L1 a mark of immunosuppression, it becomes a possible target for blocking;
2) Adoptive NK cell therapy, since obese have low NK cell number and activity;
3) Inhibition of IL-6 or its receptor related to a tumorigenic pathway;
4) Inhibition of CCL2/CCR2 and CSF/CSF-1R related to macrophage type 2 polarization and accumulation, also favoring stem cell properties development;
5) Blocking of myeloid-derived suppressor cells that also express PD-L1 and are stimulated by obesity-related cytokines; and
6) TGF-β1 blocking since its increment in obese individuals hinders a sustained effective T cell response against tumor cells[24].

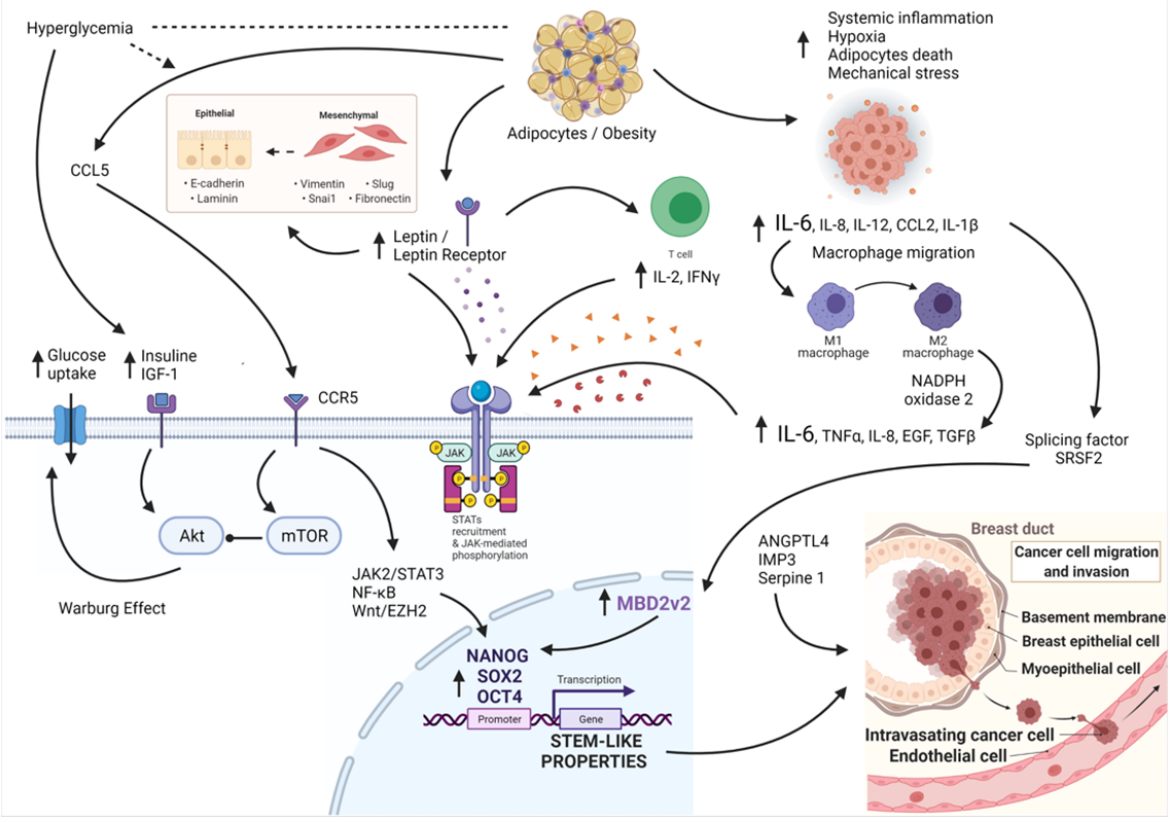

Figure 2. Pathways linking obesity and breast cancer development (created with BioRender).

DISCUSSION

After some years of research and many studies focused on exploring the specific effect of obesity on TNBC development and progression, we are beginning to identify concordant results that point to the establishment of initial consistent knowledge on this topic. In the past, breast cancer was considered a unique disease. Today, we understand that different subtypes make breast cancer notably a heterogeneous disease.

Concerning TNBC, the majority of studies agree that obesity is a risk factor for tumor development. Just one study focused on evaluating menopausal status directly, and it suggested that this association is limited to the premenopausal period[10]. The authors gave no hypothesis to explain why the prejudicial effect of obesity would be reduced after menopause, especially considering its supposed independence from hormone influence.

A temporality bias, however, could be a reasonable hypothesis. TNBC presents itself as an early-onset tumor, possibly based on the significant influence of genetic factors. Thereby, incidence at older ages would naturally be lower, as most susceptible individuals had already developed and manifested it at a younger age. Also, a higher incidence of obesity and TNBC among African-Americans should be considered as a possible bias regarding the influence of confounding genetic and social factors in this population.[4,7]

Mamidi et al. identified the main pathways activated in premenopausal women with TNBC in a whole genome transcriptome analysis, including unfolded protein response, endoplasmic reticulum stress, B cell receptor, and autophagy signaling[50]. Despite that, more investigation should be conducted to explain the possible influence of hormonal status on these specific mechanisms. As for hormone receptor-positive breast cancer, it is valid that the opposite association is observed: obesity showed itself as a protective factor among premenopausal women. Potischman et al. suggested that in premenopausal women, obesity is associated with a more significant number of anovulatory cycles, thus, lower estradiol levels and less incidence of hormone-dependent tumors[51].

Inflammation is a new focus of interest for all diseases epidemiologically associated with obesity. Pathophysiology studies revealed a world of obesity-related inflammatory and genetic cascades that could justify developing cancers independently of estrogen, such as TNBC. Almost all of the articles consisted of *in vivo* research and elucidated different pathways that could be more investigated to offer new potential therapeutic targets.

Studies related to obesity and TNBC prognosis presented conflicting findings. The authors do not exclude possible bias considering the aggressiveness of this tumor subtype. Once this cancer is established, its progression is possibly little or nothing different comparing an obese or not-obese environment. However, some authors found a worse prognosis, especially in premenopausal groups. This condition may be associated with significant incidence of TNBC in premenopausal obese women.

Concerning the still absence of specific treatment, lifestyle modifiable factors have been evaluated. Sun et al. pointed to the maintenance of an optimal body weight as a valuable primary prevention for TNBC — the only clear, effective measure currently available[52].

Even though obesity seems to favor the development of TNBC, studies investigating weight loss as a possible factor for tumor control after diagnosis did not reach concordant conclusions; tumor stage, chemotherapy side effects, or diet may influence weight loss. Further investigation in more homogeneous groups is necessary to differentiate cases in which diet and consequent weight loss could be used to break the disease from those in which weight loss occurs due to advanced tumor itself or palliative treatment. Weight loss could contribute to the reduction of hormones and inflammatory cytokines that eventually figure as stimulants for tumor cell perpetuation.

The impact of physical activity still needs to be specifically better evaluated for TNBC. Few studies analyzed it as a risk reducer for this tumor incidence. No consistent evidence has been observed, as it was reported by The Women's Health Initiative concerning breast cancer in general[53].

The complexity of inflammatory pathways and immune system regulation is a current challenge and an opportunity for improving or developing treatment for different types of cancer. Little literature is currently available, but specific targets for obese-related environmental factors seem promising, including leptin, IL-6, PD-1/PD-L1, and NK cells.

As a qualitative review, we emphasize that this study presents the risk of bias related to a subjective joint analysis of articles. The absence of a meta-analysis weakens the power of its evidence. Results remain based on the global impression of a team of experts over a systematic selection of studies.

CONCLUSIONS

There is consistent evidence supporting obesity as a risk factor for TNBC. Inflammatory cytokines related to an obese environment may contribute to tumor development. It is uncertain if the premenopausal status is a worsening factor. Obese patients with already diagnosed TNBC have a similar prognosis to t non-obese ones, and their weight loss does not seem to be a disease course modifier. Few target drugs directed to obesity-related tumorigenic pathways began to be tested and showed initial encouraging results. More investigations concerning the pathophysiology and new treatment possibilities need to be performed.

AUTHORS' CONTRIBUTIONS

LLI: data curation, formal analysis, visualization, writing – original draft, writing – review & editing. SRM: investigation, software, writing – review & editing. JRF: funding acquisition, resources, supervision, validation. EB: funding acquisition, project administration, resources. SMO: conceptualization, methodology, project administration.

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REVIEW ARTICLE
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The influence of germline mutations on breast cancer

Maria Fernanda Sperotto Valadares Gontijo[1]*, Luísa Lazarino[1], Caroline Avelar[1], João Pedro Apolinário[1], Henrique Galvão[1], Anna Dias Salvador[1], José Tadeu[1]

ABSTRACT

The ability to evade protection mechanisms and uncontrolled cell growth can lead to the development of mutations, whether somatic or germline, and consequently to the dreaded diagnosis of cancer. Breast cancer is considered the most common type of cancer in women in several regions of Brazil, mainly in the South and Southeast, second only to non-melanoma skin cancer. Approximately 5% to 10% of neoplasms are related to germline alterations that lead to hereditary predisposition. There is evidence of an association with mutations in nine genes, the highest risk being breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2). Due to its epidemiological importance, in this narrative review we observed the main genetic mutations and syndromes associated with breast carcinoma, the recommendations for screening in high-risk patients, and the indication for genetic counseling. Bibliographic research on the PubMed and Cochrane databases and analysis of the *Guidelines Breast Cancer Risk Reduction* and *Breast Cancer Screening and Diagnosis*, from June 2022 to September 2023. In this review, we observed a greater influence of germline mutations on breast cancer related to the genes BRCA1, BRCA2, PALB2, PTEN, CDH1, STK11 and, in Brazil, considered a country of ethnic-racial diversity, to TP53. As cancer screening in the country is opportunistic, knowledge of germline mutations associated with breast cancer offers specific screening recommendations for high-risk patients, indications for genetic counseling, and guidelines for prophylactic surgery, in addition to impacting the formulation of public screening policies.

KEYWORDS: genetic predisposition to disease; germ-line mutation; breast neoplasms; genes; genes, BRCA1; genes, BRCA2.

INTRODUCTION

The human genome is composed of approximately 20 to 25 thousand genes, capable of producing functional molecules, and are considered the units of genetic information. This production results from the processes of transcription and translation[1].

Exposure to various endogenous and exogenous factors can generate changes in DNA, causing the so-called mutations[2], which can occur in somatic or germline cells. There are protective mechanisms capable of correcting them, but when these mechanisms are ineffective, they lead to the development of malignant cells[3].

Female breast carcinoma is prevalent in all regions of the country, mainly in the Southeast and South, second only to non-melanoma skin cancer. An estimated 73,610 new cases were reported each year in the 2023–2025 triennium. The risk increases with age, but it has been observed that the number of young patients diagnosed with the disease has exponentially increased[4].

Researchers indicate that between 70% and 80% of breast carcinomas are related to environmental factors and 5% to 10% to germline genetic alterations[5].

When a pathogenic germline variant alone is associated with a significantly increased risk of cancer, it is a hereditary predisposition syndrome. Most of these syndromes result from a mutation in one of the two alleles of a given gene present in the genome. Therefore, they present an autosomal dominant inheritance pattern, with a 50% risk of transmission to offspring[6].

Risk stratification for the development of breast cancer in a consultant depends on a detailed anamnesis, starting from personal history, analyzing factors such as age, habits, sedentary lifestyle, smoking, alcohol use, gynecological and obstetric history, personal and family history of cancer in first-degree relatives. In addition, there are mathematical models that quantify the risk of breast cancer, the most widely used being those of Gail and Tyrer-Cuzick[7].

Authors of a recent publication by the Breast Cancer Association Consortium found strong evidence for the association of pathogenic variants in nine genes with breast cancer risk. The genes considered high risk are TP53, BRCA1, BRCA2, PALB2, and ATM; BARD1, CHEK2, RAD51C, and RAD51D are moderate risk. ATM

[1]Mater Dei Rede de Saúde – Belo Horizonte (MG), Brazil.
***Corresponding author:** mariafernandasperotto@gmail.com
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and CHEK2, in turn, are related to estrogen receptor-positive breast cancer, and the others, to hormone receptor-negative[8].

Pathogenic variants in BRCA1 and BRCA2 are the most common, being associated with almost 50% of the risk attributable to the family component for the development of the disease. These patients have a cumulative increase in the risk of invasive breast cancer, from 55% to 85%, up to the age of 70 years and a 15% to 65% increase in the risk of developing ovarian cancer[8].

It is worth familiarizing oneself with other hereditary diseases, such as Li-Fraumeni syndrome (mutation in the TP53 gene), Cowden syndrome (PTEN), and those in which other sites of involvement are more common, but which also present a risk for breast cancer such as Peutz-Jeghers syndrome (STK11) and hereditary diffuse gastric cancer (CDH1)[9].

Due to their epidemiological importance, in this study we described the main genetic mutations and syndromes associated with breast cancer and the risks of developing the disease as well as screening recommendations, strategies for early diagnosis, classification of high-risk patients, and genetic counseling.

The main objective of the study was to identify the importance and influence of germline genetic mutations on breast cancer in the literature. As secondary objectives, we sought to outline strategies for tracking the disease in the high-risk population.

METHODS

For this narrative review, the bibliographic research was based on the described objectives. The starting point consisted of the questions: what is the importance of the hereditary component in the risk of breast cancer? What syndromes are most associated with breast cancer? What are the risks of a person with a hereditary predisposition developing breast cancer? What are the screening strategies for patients classified as high risk? Searches were conducted on the PubMed and Cochrane databases and analysis of the *National Comprehensive Cancer Network Breast Cancer* (NCCN), *Guidelines Breast Cancer Risk Reduction*, and *Breast Cancer Screening and Diagnosis*, from June 2022 to September 2023.

RESULTS AND DISCUSSION

The human genome is composed of DNA, and we are exposed daily to several endogenous and exogenous factors capable of affecting and changing our genetic code, giving rise to somatic or germline mutations[10]. Somatic, or acquired, mutations occur during DNA replication, preceding a mitotic division, and are generally limited to a specific tissue. They affect all cells generated from the mutated cell, and this mechanism is one of the hallmarks of cancer. Germline cells occur during DNA replication, preceding meiosis. The mutation affects gametes and all cells that originate from them and are transmitted to offspring[10].

Breast cancer is categorized into subtypes based on molecular identification from immunohistochemical evaluation. In this process, the presence or absence of hormone receptors (estrogen and progesterone) and overexpression of the HER2 protein are identified. Perou and Sorlie (2000) developed *in situ* hybridization techniques for detecting HER2 amplification, leading to greater accuracy in dividing breast cancer into four subgroups[11]:

- Luminal A (KI 67, which corresponds to a cell proliferation index<10%);
- Luminal B (KI 67>10%);
- HER2 overexpressed (3+);
- Triple-negative (tumor without all three standard molecular markers).

Although most neoplasms are the result of complex interactions between the genetic component and the environment, a percentage of cases can be attributed to inherited genetic alterations, which lead to a greater predisposition to the development of tumors. Currently, it is estimated that approximately 5% to 10% of carcinomas are associated with hereditary predispositions such as breast, prostate, colorectal, and pancreatic cancer. Furthermore, certain tumors that occur predominantly in childhood may be hereditary, as is the case with retinoblastoma, considered the paradigm of familial cancer[12].

There are support tools, such as mathematical models, that can be used to numerically predict the risk of breast cancer. The most widely used are the Gail, Claus and Tyrer-Cuzick models. The Gail model is the best known and focuses primarily on personal background, but is limited to family background. The Claus model focuses almost exclusively on family background. Conversely, the Tyrer-Cuzick model is the one that covers information the most[13].

Gail assesses the risk of breast cancer occurring in the next five years, reaching the age of 90 (lifetime risk). Using this method, eligibility for the use of tamoxifen is calculated (greater than 1.67% in five years). The Claus model assesses the lifetime risk of breast cancer and determines eligibility for breast MRI (greater than 20%). Tyrer-Cuzick assesses the ten-year risk of breast carcinoma and polygenic genetic inheritance and guides genetic counseling in patients with a lifetime risk above 20%.

Genes associated with hereditary breast cancer are subdivided into high-risk genes (relative risk – RR>or equal to 5), moderate-risk genes (RR>or equal to 1.5 and<or equal to 5), and low-risk genes (RR<or equal to 1.5)[8,14].

In the last decade, significant advances have been made in the knowledge of molecular mechanisms that give rise to cancer, identifying several genes directly involved in the development of neoplasias, including oncogenes (which predispose to cancer when overexpressed), tumor suppressor genes (which can give rise to a tumor when inactivated), and genes of the DNA repair system (inactivation leads to the accumulation of mutations). This culminated in the identification of genes associated with specific hereditary cancer predisposition syndromes[15].

The most frequently mutated genes are BRCA1 (27.4%), BRCA2 (20.3%), TP53 (10.5%), ATM (8.8%), CHEK2 (6.2%), and PALB2 (5.1%) (Figure 1). BRCA1 and BRCA2 account for approximately 50% of all pathogenic/likely pathogenic germline variants. The multigene panel was responsible for doubling the identification of germline variants in predisposition genes other than BRCA1 and BRCA2 as well as increasing the chance of finding a variant of unknown significance (VUS) by 12 times[16].

Genes considered moderate risk, which increase the risk of breast cancer by at least two times, are identified in 2% to 3% of women diagnosed with breast carcinoma and in approximately 1% of the general population. ATM, CHEK2, and PALB2 are the most common in this subgroup[17].

For ATM and CHEK2 variants, odds ratios were higher for breast cancer with estrogen receptor-positive disease than for hormone receptor-negative disease. For BARD1, BRCA1, BRCA2, PALB2, RAD51C, and RAD51D variants, odds ratios were higher for estrogen receptor-negative than for hormone receptor-positive disease[18].

Among the high-risk syndromes, we can mention hereditary breast and ovarian cancer (HBOC), related to BRCA1 and BRCA2. Female patients with a BRCA1 mutation have a risk of approximately 70% of developing breast cancer by the age of 80 and a 9% to 20% risk of developing a second breast cancer. In patients with a BRCA2 mutation, the risk remains the same until the age of 80, but the risk of developing a second cancer within five years is reduced by 3% to 12%. The risk of developing ovarian cancer by the age of 70 in patients with a BRCA1 mutation is approximately 44% and with a BRCA2 mutation, 17%[9].

Li-Fraumeni syndrome is also mentioned, associated with a germline mutation in the TP53 gene, in which international case studies estimate a risk of up to 90% of carriers developing cancer by the age of 60. When developing breast cancer, the risk would be approximately 85% by the age of 70. The syndrome is considered to be at high risk for the development of multiple primary tumors[16].

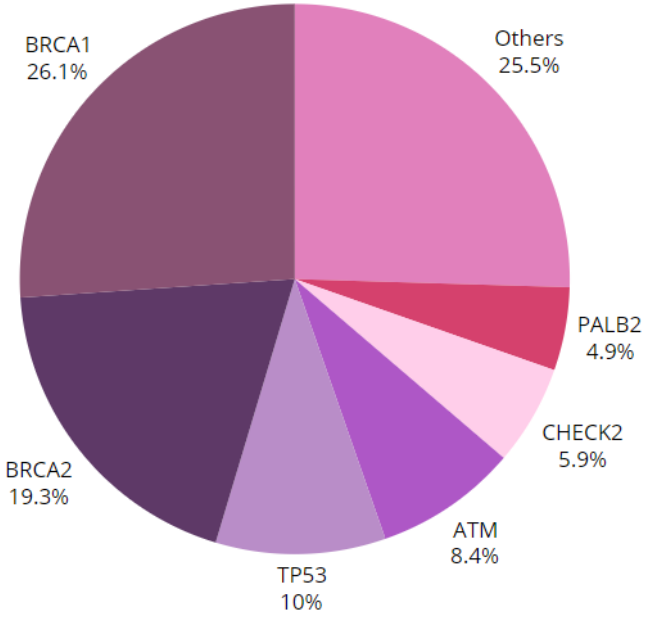

Figure 1. Graph with the main genes related to breast cancer and their frequency.

In Brazil, special attention should be given to the p.(Arg337His) variant in the TP53 gene. It is estimated that it is found in around 2.7 out of a thousand individuals born in the Southern region of the country. Researchers associate a more aggressive phenotype of Li-Fraumeni, with a mutation in an expression-modifying gene, XAF1. As a consequence, the high prevalence of this variant in TP53 significantly impacts screening strategies and risk reduction in the country[19].

Knowledge of genetic mutations related to breast cancer predisposition has a strong impact on the creation of screening and early diagnosis strategies.

According to the NCCN, screening for patients with BRCA1 and BRCA2 mutations begins at the age of 25, with a biannual clinical examination and annual breast MRI, and at age of 30, with annual mammography and MRI. According to the North American organization, risk-reducing mastectomy or prophylactic tamoxifen should be considered; salpingo-oophorectomy should be indicated as of the age of 35 in BRCA1 and as of the age of 40 in BRCA2; and, above the age of 75, management should be individualized.

For men, an annual clinical breast exam is recommended as of the age of 35 and mammography should be considered at the age of 50 or ten years before the earliest diagnosis in the family. For patients with TP53 mutation, breast screening is recommended as of the age of 20, with biannual clinical examination and annual MRI, and as of the age of 30, annual breast MRI and mammography[20,21].

Genetic testing to assess susceptibility to breast cancer has been an important aspect of disease prevention. Since the 1990s, with the description of the BRCA1 and BRCA2 genes, there has been a continuous improvement in guidelines for screening for breast cancer and reducing the risk for high-risk women and their families[22].

Genetic counseling is a fundamental part of the national cancer policy, being responsible for identifying individuals at high risk of developing tumors. This is the communication process that deals with the problems associated with the occurrence or possibility of a genetic disorder occurring in a family. Families with multiple cases of cancer, bilateral tumors, or tumors diagnosed at very early ages compared to the average age of diagnosis in the general population should be referred to genetic counseling. Among the foundations of this counseling are:

- voluntary use of services;
- informed decision-making;
- nondirective and noncoercive counseling;
- protection of privacy and confidentiality of genetic information;
- attention to psychosocial aspects associated with the impact and management of genetic information[9].

During a genetic evaluation, the patient's ancestry and region of origin must be taken into account. Individuals with *Ashkenazi* Jewish ancestry, for example, have a higher prevalence of mutations in the BRCA1 and BRCA2 genes, given that one in every 40 patients (2.5%) carries the mutation compared to one in every 400 patients (0.25%) in the general population[9].

In genetic counseling, risk-reducing surgeries, traditionally known as prophylactic surgeries, are considered prevention strategies. This term should be used with caution, as it suggests the false idea that mastectomy guarantees total prevention against breast cancer. This procedure may be indicated for high-risk patients, however, its role is better defined in women carrying deleterious mutations, especially BRCA1 and BRCA2. These surgeries are highly complex and have a considerable risk of complications, and should therefore be reserved for special situations and after careful assessment of risks and benefits in a multidisciplinary environment[23].

In the guideline published in 2024 by the American Society of Clinical Oncology (ASCO)[24], germline genetic testing is recommended for any patient up to 65 years of age who is newly diagnosed with breast cancer or has a history of this neoplasia, regardless of family history. This will allow patients to seek genetic counseling, allowing changes to be made in the way they and their families are monitored. It is also recommended that all patients with a history of breast cancer diagnosed over the age of 65 with any of the following criteria be tested:

1. Personal or family history suggesting the presence of a pathogenic variant;
2. Patient with triple-negative breast cancer histology;
3. Male patient;
4. Patient of *Ashkenazi* Jewish descent or member of a population with a higher prevalence of founder mutations.

In Brazil, Bill No. 265/2020 is currently being processed in the National Congress, which amends Law No. 11.664/2008, which provides for the implementation of health actions that ensure prevention, detection, treatment, and follow-up of cervical and breast cancers within the scope of the Brazilian Unified Health System (SUS), to also ensure tests for detecting genetic mutations[25].

The right has already been assisting women in the supplementary system operated by health insurance plans since 2014. In 2015, through the law known as the "Angelina Jolie Law," an agreement was signed between the government of Rio de Janeiro and the SUS for tests to detect genetic mutations of the BRCA1 and BRCA2 genes in women with a family history of neoplasia diagnosis. In 2019, Minas Gerais was the second Brazilian state to formulate legislation with the same purpose, followed by the states of Goiás, the Federal District, and Amazonas.

The NCCN 2024 includes the possibility of risk-reducing mastectomy for women carrying mutations in other genes, such as TP53, PTEN, PALB2, and salpingo-oophorectomy for those with mutations in RAD51C, RAD51D, and BRIP1. The first consistent data regarding the benefit of risk-reducing surgery in women at high risk for breast cancer come from the study by Hartmann et al., which showed a risk reduction after 14 years of follow-up in 90% of cases[26].

A study published in the Breast Cancer Research and Treatment in 2019 evaluated 2,857 asymptomatic women carrying a BRCA1 or BRCA 2 mutation and the benefit of risk-reducing surgery. At the end of the average follow-up of ten years, there were 268 cases of breast cancer in the BRCA1 group, which did not undergo surgery, and a higher mortality rate compared to those patients who underwent surgery (99.7% *vs* 93.2%, p=0.002)[21].

In view of the complexity of hereditary cancer in public health programs in 1996, in the USA, the National Cancer Institute (NCI) proposed the creation of a national cancer genetics network through the joint effort of doctors and researchers from various health institutions. The Cancer Genetics Network (CGN) was officially announced in September 1998 as a network of eight centers specializing in the study of hereditary predisposition to cancer[27].

CONCLUSIONS

The Brazilian population has unique ethnic characteristics. The miscegenation observed in the country offers an opportunity to advance in the understanding of the genetic characteristics of cancer without the bias of studies with isolated populations[28].

Identifying individuals with a higher genetic susceptibility to developing neoplasms is important, considering that there are education, screening, and risk reduction measures that can be indicated for this specific group[12]. Screening strategies should be followed with clinical and imaging tests in patients of all social conditions.

In Brazil, there are still few public or private actions aimed at identifying, guiding, and monitoring individuals and families at high risk for hereditary cancer. Larger and more prospective studies are necessary to observe and measure more effective interventionist — or even observatory — methods with greater certainty of execution.

AUTHORS' CONTRIBUTION

MFSVG: Conceptualization, Literature review, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. LLSC: Data curation, Formal analysis, Writing – review & editing. CA: Formal analysis, Investigation, Writing – original draft. JPCA: Validation, Writing – review & editing. HRG: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. ADS: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. JTCA: Conceptualization, Project administration, Methodology, Visualization, Writing – original draft.

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CASE REPORT
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Malignant phyllodes tumor of the breast in ayoung patient – case report

Cássio Furtini Haddad[1]*, Ana Carolina de Oliveira Paiva[1], Juan Pablo de Souza Silva[1], Isabela Teixeira Rodrigues[1]

ABSTRACT

ABSTRACT: Phyllodes tumor (PT) is an uncommon form of breast tumor. It occurs most commonly in women aged 35 to 65 years. The benign form represents about 85–90% of cases and only 10–15% of PTs are malignant. Clinically and radiologically, malignant phyllodes tumor (MPT) presents as regular, well-delimited, mobile nodules that are difficult to distinguish from fibroadenomas of the breast. The most important differential diagnoses of MPT include fibroadenoma, metaplastic carcinoma, and sarcoma. The prognosis of MPT exhibits a higher frequency of local recurrence and metastatic rate with larger tumors and inadequate surgical margins. The case presented here refers to a 24-year-old female patient, with a vast tumor in the right breast, with rapid and progressive growth, associated to local pain, and histological diagnosis of MPT. Surgery was the initial treatment, followed by adjuvant chemotherapy and radiotherapy. The purpose of this article was to report an atypical case of MPT of the breast in a very young woman as well as to make a brief literature review on this infrequent and dangerous disease.

KEYWORDS: phyllodes tumor; malignant phyllodes tumor; breast neoplasm; case reports.

INTRODUCTION

Phyllodes tumor (PT) of the breast is uncommon, representing 0.3–1.0% of all breast neoplasms and 2.5% of all fibroepithelial breast tumors[1,2]. The estimated incidence is 2.1 cases per million women[2].

It occurs most commonly in women aged 35 to 65 years. The benign form represents about 85–90% of cases. Only 10–15% of PTs are malignant (MPTs), and only 10–26% of MPTs are found with metastasis[3].

The presence of a painless unifocal mass with a history of fast growth, reaching a large size, and in advanced age may be clinical findings favorable to the diagnosis of the PT[3]. Tumor size can vary between 1–45 cm, with an average size of 4–5 cm, although MPTs can reach larger dimensions[3,4]. There are no specific clinical manifestations to distinguish benign from malignant subtypes[1].

The World Health Organization classifies these tumors as benign, borderline, or malignant according to a combination of histological features, including stromal cellularity, nuclear atypia, mitotic activity, stromal overgrowth, and tumor margin[1,3].

Clinically and radiologically, they present as regular, well-delimited, mobile nodules that are difficult to distinguish from fibroadenomas of the breast.

Surgery is the standard treatment. Generally, local excision is performed for benign and small tumors, while total mastectomy is considered for borderline, large, malignant, and recurrent tumors. Overall, segmental resection with adequate margins is the treatment of choice[5]. The role of radiotherapy and chemotherapy remains controversial. Adjuvant radiotherapy has been shown to increase disease-free survival in MPTs treated with segmental resection. However, available data on increased overall survival in the literature are inconclusive[6].

This article aimed to report a case of MPT of the breast in a very young woman as well as to make a brief literature review on this infrequent and dangerous disease.

CASE REPORT

This is a 24-year-old female patient referred for evaluation of a nodule in the right breast, with rapid and progressive growth, for about two months, associated with local pain. Nulligest, without comorbidities or use of medication, she had a history of bilateral reduction mammaplasty eight years ago. Family history revealed

[1]Universidade Federal de Lavras, Department of Health Sciences, Department of Medicine – Lavras (MG), Brazil.
*Corresponding author: cassiohaddad@hotmail.com
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two maternal great-aunts with breast cancer. On clinical examination, the patient presented a bulging and voluminous nodule in the upper lateral quadrant (ULQ) of the right breast, measuring 8.0 x 6.0 cm, with fibroelastic consistency and mobile; and non-palpable axillary lymph nodes. Ultrasound image evidenced a large oval, regular, and circumscribed mass, containing aneugenic areas inside, measuring approximately 7.0 x 6.0 x 5.0 cm in the ULQ. Breast magnetic resonance imaging showed a solid-cystic, oval, heterogeneous nodule with indistinct margins, early enhancement, and predominantly peripheral, in the ULQ/axillary extension of the right breast, measuring 7.0 x 5.0 x 4.0 cm, without plane of clear cleavage between the nodule and the pectoralis major muscle, in addition to right axillary adenopathy - Breast Imaging Reporting and Data System (BI-RADS 4®). A core biopsy of the lesion was performed, with anatomopathological findings: pleomorphic neoplasm with a tubulosarcomatoid disposition, with the possibility of a MPT.

Subsequently, the patient evolved with rapid lesion growth, significant local pain, and skin suffering in the region of the lesion (Figure 1). Chest and abdomen tomography showed no relevant changes. Surgical treatment was indicated and, after discussing the case, the patient opted for conservative surgery. Thus, a partial mastectomy was performed, with resection of the tumor with margins of the pectoralis major muscle fibers due to tumor infiltration, and of enlarged lymph nodes in the right axillary region, associated with the creation of a glandular and cutaneous flap for closure (Figures 2 and 3). Anatomopathological and immunohistochemical results revealed high-grade pleomorphic/spindle cell malignancy, with myogenic differentiation, measuring 7.5 x 7.0 x 4.5 cm, free margins, and absence of metastasis in the five dissected lymph nodes, with a probable diagnosis of MPT.

Finally, patient recovered well in the postoperative period, with preserved right upper limb mobility, and, after evaluation of clinical oncology, adjuvant chemotherapy with six cycles of doxorubicin and ifosfamide was indicated. Adjuvant radiotherapy was performed with a hypofractionated protocol of 15 sessions, and a concomitant boost in the surgical area (total dose of 40 Gy in the breast and 48 Gy in the operative site). Germline genetic panel was not performed. Before the chemotherapy treatment, the medical team discussed with the patient and a fertility preservation technique was performed, through ovulation induction with gonadotropins and oocyte collection for cryopreservation.

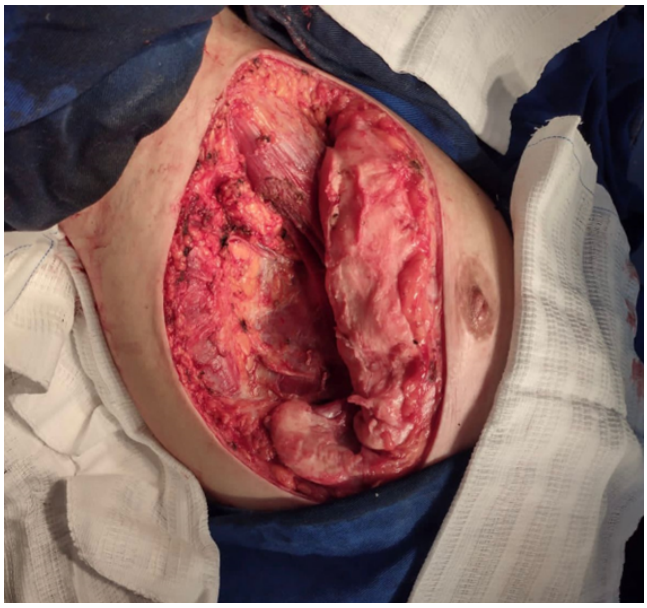

Figure 2. Intraoperative – post-tumor resection.

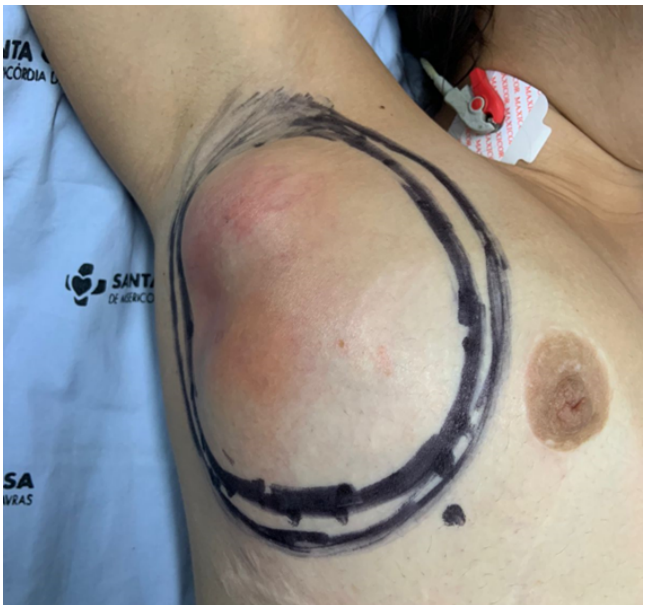

Figure 1. Tumor clinical presentation.

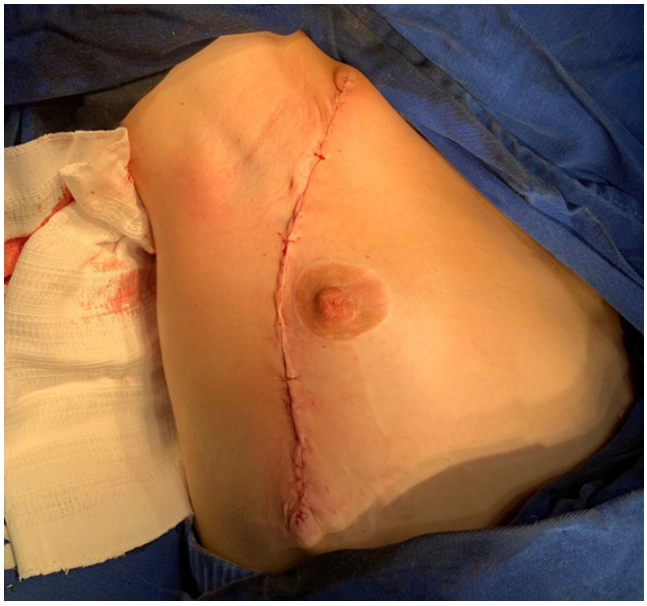

Figure 3. Intraoperative – post-final suture.

DISCUSSION

PT is a rare form of breast tumor. It was first described by Johannes Muller in 1838 and constitutes 0.3–1.0% of all breast tumors[1]. MPTs are extremely rare and can imitate benign tumors such as fibroadenomas on clinical examination. The median age for presentation of MPT is 50 years old[7].

Regarding histopathological aspects, PTs are defined as a group of circumscribed biphasic tumors, similar to fibroadenomas, composed of periductal stroma and ductal epithelium, with a double-layered foliar growth pattern with hypercellular stroma, characterized by pleomorphism and stromal overgrowth, infiltrative borders, and usual mitoses[1,2]. Clinically, the most common finding is the breast lump — mobile and painless. Dilated veins can be seen overlying large PTs. Axillary metastases are uncommon, and most palpable axillary lymph nodes are reactive, not metastatic[8].

Diagnosis should preferably be made by histopathological study, obtained by core needle biopsy or excisional biopsy. Fine needle aspiration (FNA) does not provide the information necessary for a differential diagnosis. Due to the similarity of cytological features for benign PT and cellular fibroadenoma, these two biphasic fibroepithelial lesions cannot be properly differentiated on FNA[9]. A PT with a bland stromal component can mimic a fibroadenoma; whereas a PT with a stroma that appears overtly sarcomatous can be challenging to differentiate from a sarcoma. MPT is defined by the combination of marked nuclear pleomorphism of stromal cells, stromal overgrowth (defined by the absence of epithelial components in one low-power microscopic field), diffuse stromal cellularity with increased mitotic activity (>10 per 10 HPF [high-power fields]), and infiltrative borders[3]. The most important differential diagnosis of MPT includes fibroadenoma, metaplastic carcinoma, and sarcoma[10]. The immunohistochemical findings are characterized by the expression of p53, CD117, p16, EGFR, Ki-67, and VEGF, which reveal low positivity in benign PT and high in MPT[11].

Although PT is primarily treated by surgical excision, literature data demonstrate that all PTs can recur regardless of their histology, with lower incidences of recurrence evidenced in benign tumors and higher rates observed in borderline and malignant ones. Local recurrence (LR) rates vary by 15–40% among different types of PT[12]. The risk factors most commonly associated with LR comprehend not only positive margins but also the existence of necrosis, stromal overgrowth, and a larger tumor size. No difference was found in terms of LR among patients undergoing mastectomy or breast-conserving surgery[7]. Our patient underwent partial mastectomy and margins were free on anatomopathological analysis. A large retrospective and multicenter study on MPT management demonstrated that a 3 mm margin threshold was appropriate, with no impact of larger margins on overall survival. Hence, they recommended re-excision to achieve wider margins in cases with 0–1–2 mm margins[13]. The National Comprehensive Cancer Network (NCCN) guideline recommends wide excision with clean margins ≥1 cm for MTP[14]. Axillary lymph node dissection showed no added benefit on the recurrence or disease-free survival in MPT. Most lymphadenopathy in MPT is usually either reactional to tumor necrosis or to infected ulcerated skin lesions, with less than 1% of pathological involvement[15].

The role of adjuvant radiotherapy in MTP is still controversial. Several studies have shown that radiation therapy is associated with reduced LR but did not have any impact on overall survival[16]. The use of adjuvant chemotherapy is more questionable and its effect on PTs is doubtful. Adjuvant cytotoxic chemotherapy lacks evidence of benefits both for reducing LRs and for improving overall or disease-free survival. Owing to the low frequency of distant metastasis, only a small number of retrospectively analyzed cases have been reported and a treatment strategy for MPT has not been established. Nevertheless, it can be considered for large tumors, when adjacent structures such as the chest wall are involved, or unresectable distant metastasis[17]. In these cases, chemotherapy regimens of soft tissue sarcomas are generally employed. NCCN guideline recommends anthracycline plus ifosfamide as the first line of treatment[14]. Although pathologically, they express estrogen receptors in 58% and progesterone receptors in 75% of cases; endocrine therapy has not proven to be beneficial in the treatment of PTs[18].

The prognosis of MPT exhibits a higher frequency of LR (12–65%) and metastatic rate (up to 27%) with larger tumors and inadequate surgical margins[13]. The most common spots for metastasis are the lungs, pleura, and bone. The 5-year survival is around 65%[7]. Kapiris et al. reported a 5-year survival rate of 54% and a 10-year survival rate of 23%, with a significant association of results according to tumor size and surgical margins[12].

Germline genetic panel is not routinely ordered for patients with PT. The NCCN practice guidelines do not include PT as criteria for genetic counseling or as testing criteria for any of the known heritable cancer syndromes[14]. Recently, in a multi-center contemporary cohort of 550 PTs, Rosenberger et al. found that roughly 10% of PT patients tested for germline cancer predisposition genes carried a deleterious mutation, similar to that seen among women with breast adenocarcinoma[19].

CONCLUSIONS

MPTs are rare entities. These tumors should be correctly recognized and effectively treated at first diagnosis since they have an elevated risk of recurrence. The PT diagnostic hypothesis should be raised in tumors with benign characteristics, rapid growth, and large dimensions. Accurate pathological classification of PTs is relevant to foresee the risk of recurrence and survival rate. Benign and borderline PTs have less aggressive disease behavior

than MPT. Excision with adequate margins is the recommended therapy. There is no stated consensus concerning the optimal type of surgery and indications for radiotherapy and chemotherapy in these cases. The establishment of adequate and standardized therapeutic strategies for MPTs is needed to reduce the risk of local and distant tumor recurrence.

AUTHORS' CONTRIBUTION

CFH: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. ACOP: Investigation, Validation, Writing – review & editing. JPSS: Formal analysis, Investigation, Writing – original draft. ITR: Formal analysis, Investigation, Writing – original draft.

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CASE REPORT
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A Rare Case of Syringomatous Tumor of the Nipple and Breast Reconstruction

Juliana Lopes de Aguiar Araújo[1], Ubiratan Wagner de Sousa[1], Macerly Laise de Menezes Dantas[1], Waleria Pimper[2], Diana Taissa Sampaio Marinho Navarro[1]*

ABSTRACT

Syringomatous tumor, first described in 1983, is a rare benign clinical condition that can affect the breast. Its infiltrative form is often misidentified as malignant pathologies, as it can present as a subareolar lesion with suspicious clinical, mammographic, and ultrasound findings for malignancy. The exact origin of these lesions remains uncertain; however, they may manifest as a unilateral or bilateral subareolar nodule with symptoms such as pain, edema, nipple enlargement, and nipple discharge. Despite local infiltration, there is no evidence of regional or distant metastases. Local complete excision appears to be an adequate therapy, with only cases that were incompletely excised showing recurrence. Below is a case report of a syringomatous adenoma infiltrating the nipple, with complete resection and nipple reconstruction using oncoplastic techniques.

KEYWORDS: breast reconstruction; breast tumor; breast neoplasms.

INTRODUCTION

The areola-nipple complex (ANC) is the origin of various morphologically distinct tumors and related changes, stemming from the unique structures of the nipple, especially the intramammillary ducts, adjacent structures, and intramammillary stroma[1]. The syringomatous tumor of the nipple, a rare benign condition[2], was first described by Rosen in 1983[3].

Although benign, its tendency to infiltrate locally and recur if not completely excised can lead to it being mistaken for a malignancy.

The disease typically presents as a unilateral or bilateral subareolar nodule, accompanied by clinical manifestations such as erythema, pain, edema, nipple distension, and papillary discharge[4]. This case report aimed to address both the rarity of the condition and the significance of differentiating it from breast neoplasms, as well as to describe an alternative technique for nipple reconstruction.

CASE REPORT

A 55-year-old female patient, who experienced menarche at 11 years old and has had three children, her first at age 20, with breastfeeding lasting for 8 months. She had been using hormonal contraceptives for 12 years. She had been regularly consulting a mastologist to monitor nodules since March 2021. A mammogram (MMG) in November 2022 revealed nodular images and focal asymmetries (BI-RADS 3). An ultrasonography (USG) performed the same month showed a heterogeneous area of 2 cm at 9 o'clock and 4 cm from the nipple, which could correspond to either breast tissue or a solid nodule in the right breast (NRB), and another NRB of 0.8 cm at 6 o'clock and 3 cm from the nipple (BI-RADS 3); these nodules had been stable since August 2022. A fine needle aspiration (FNA) of the NRB at 9 o'clock revealed rare groups of typical ductal cells. During a routine consultation in November 2022, increased hardness was observed in the right nipple, covering more than two-thirds of its surface (Figure 1).

A magnetic resonance imaging (MRI) scan was requested, revealing intra-nipple enhancement in the right nipple extending 0.9 cm, categorized as BI-RADS 4. Additionally, a solid nodule in the left breast (NLB) was detected at 5 o'clock, 4.7 cm from the nipple, with a type II curve (Figure 1).

In February 2023, she underwent excision of two mammary nodules in her right breast and an incisional biopsy of the right nipple. The anatomopathological examination revealed that the nodules were fibroadenomas, measuring 1.2 cm and 0.6 cm. The nipple biopsy showed a syringomatous tumor of the nipple with compromised margins (specimen: 0.8 cm). Immunohistochemistry

[1]Liga Norte Riograndense Contra o Câncer, Institute of Education, Research and Innovation – Natal (RN), Brazil.
[2]Universidade Potiguar – Natal (RN), Brazil.
***Corresponding author:** dianataissa@msn.com
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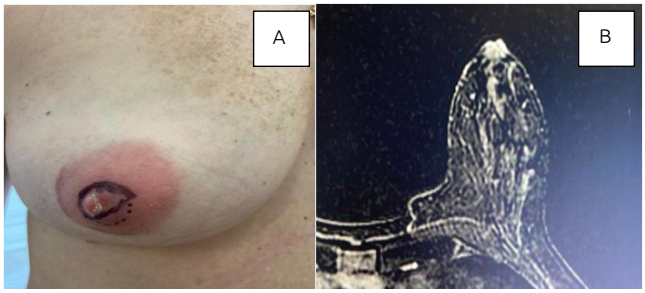

Figure 1. (A) Lesion in the right nipple affecting more than half of its volume and (B) MRI showing enhancement within the right nipple.

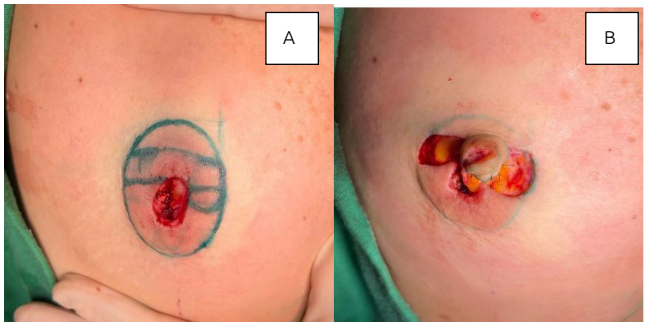

Figure 2. (A) Right breast after nipple resection with planned incision for the neomamilo and (B) assembly of the nipple after bringing the cylinder together.

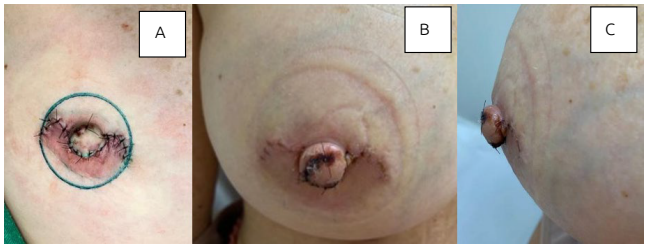

Figure 3. (A) Neomamilo after approximation of the areolar flaps to the nipple (immediate) and seventh postoperative day, (B) frontal view, and (C) lateral view.

confirmed the diagnosis, showing positivity for markers p63, cytokeratins 5/6, 14, and 8/18, estrogen receptor (ER) positive, and ki67 at 5%.

After analyzing the exams and reassessing the patient, it was decided to perform a complete resection of the tumor with margins and immediate nipple reconstruction. The surgery took place on July 20th, 2023. The entire right nipple and part of the base of the areola were resected (Figure 2).

After removing the nipple, it was sent for freezing and evaluated macroscopically, showing free margins. For nipple reconstruction using local flaps, and considering the patient did not have a contralateral donor nipple, the double-opposed periareolar/pouch flap technique was chosen. Modifications were made to the technique, positioning the upper closure portion of the nipple projection, which is normally central, laterally. The wings of the flap were marked with measurements of 1 cm in width and 1 cm at the base. Dissection began with the external wings, elevating them with a thin layer of subcutaneous fat. The papilla was then assembled and sutured together (Figure 2). The areolar flaps were sutured to the base of the papilla, and the incisions were approximated using single stitch sutures (Figure 3).

On the seventh postoperative day (POD), the areola stitches were removed (Figure 3), and on the 14th day, the stitches on the nipple were removed. The anatomopathological examination revealed a 1.5 cm syringomatous tumor of the nipple with free margins. The patient is currently scheduled for areola micropigmentation.

DISCUSSION

A syringomatous tumor typically presents as a solitary firm mass in the subareolar region or on the nipple and can occur within the breast parenchyma[2]. It may be clinically asymptomatic, sensitive, and painful on palpation, and/or present with itching and ulceration. The size varies from 1 cm to 3 cm in diameter[4]. The average age at presentation is 40 years, with an age range from 11 to 76 years[3]. Nipple inversion or discharge may be present[5]. It can be pathologically misdiagnosed as ductal breast carcinoma, which can lead to delays or errors in diagnosis. Timely management with histopathological correlation is essential, as it allows for less invasive surgical methods.

The imaging findings of a syringomatous tumor often resemble those of malignant tumors, making it difficult to distinguish from carcinoma on imaging studies such as MMG, USG, and MRI[2]. On MMG, it may appear as a high-density mass in the subareolar region with an irregular contour, spicules, or microcalcifications. On USG, it typically presents as a poorly defined mass with heterogeneous internal echoes[4]. Since fine needle aspiration or needle biopsy often fails to provide a definitive diagnosis, many cases are reported as suspected malignancies[4].

Some researchers have reported the usefulness of immunohistochemical staining for p63 or S-100 protein[5,6]. However, in the present study, staining was performed for Ki-67, a prognostic and predictive marker for breast cancer[7]. Ki-67 is expressed during the G1, S, G2, and M phases of the cell cycle but not during the resting G0 phase. Therefore, high levels of Ki-67 indicate a tumor with high proliferative potential. In other words, Ki-67 staining helps differentiate between benign and malignant tumors and predict prognosis.

The presence of a myoepithelial layer in syringomatous tumors is not completely indisputable, but it is commonly mentioned in the literature due to positive reactions for "myoepithelial cell markers" such as p63 or Ck5/6. Recently, however, immunohistological findings have demonstrated that syringomatous tumors of the nipple are p63+ Ck5/14+ proliferations of progenitor cells in the nucleus,

which differentiate into glandular (Ck8/18) and squamous cells (Ck10/13). Differentiations into myoepithelial cells (actin, CD10, calponin, etc.) are much rarer and usually only focal in these tumors. Therefore, in the context of syringomatous tumors, the expression of p63 and high molecular weight cytokeratins Ck5 and/or Ck14 cannot be used as an indication of myoepithelial differentiation[1].

Pathologically, the tumor appears grossly ill-defined, with a firm to resistant consistency and a gray or white cut surface[8]. Histologically, the lesion is composed of tubules, ducts, and strands of small, uniform, generally basophilic cells that infiltrate the dermis of the surrounding skin and the stroma of the nipple[8]. Proliferating ducts, lined by one or multiple layers of metaplastic squamous cells, may be present. These cellular nests often have a teardrop or comma-shaped appearance, and tumor cells can infiltrate the stroma between smooth muscle bundles and even into the perineural region[4].

Histologically and clinically, syringomatous adenoma of the nipple is often mistaken for tubular carcinoma or low-grade adenosquamous carcinoma of the breast. Special attention from pathologists and clinicians is crucial to avoid incorrect diagnoses and unnecessary treatments[4].

The histopathological diagnostic criteria for syringomatous tumor include:

- Location in the dermis and subcutaneous tissue of the nipple or areola;
- Irregular tubules, compressed or comma-shaped, infiltrating into bundles and/or smooth muscle nerves;
- Presence of myoepithelial cells around the tubules;
- Presence of cysts lined with stratified squamous epithelium and filled with keratinized material;
- Absence of mitotic activity and necrosis[4].

Due to its rarity, the syringomatous tumor presents an intriguing diagnostic challenge. Differential diagnoses include primary malignant breast carcinomas such as low-grade adenosquamous carcinoma and tubular carcinoma. Tubular carcinoma typically occurs deep in the breast, often located in the upper quadrant, lateral to or away from the nipple. If it extends to the nipple, it may cause nipple retraction or Paget's disease. Tubular carcinoma is also more commonly ER positive, whereas syringomatous tumors are usually ER negative. Syringomatous tumors are benign and have not been reported to metastasize. However, they can exhibit local recurrence if not completely resected[6]. Therefore, the ideal initial management involves complete resection with histologically negative margins. If the margins appear involved, reexcision is recommended.

In patients with negative margins after removal of the entire syringomatous tumor, there was no evidence of recurrence during a follow-up period of 1 to 6 years[9]. However, patients with positive margins after local surgical excision experienced tumor recurrence[10]. Therefore, careful monitoring to detect local recurrence is considered necessary[5]. Most recurrences were treated with local reexcision. However, since syringomatous tumors of the nipple generally occur in the dermal and subcutaneous regions of the nipple or areola[3]; appropriate management often requires total resection of the ANC.

If the tumor is so close to the nipple that preserving it is impossible, and the patient wishes to preserve it, an appropriate treatment regimen must be selected. In these cases, however, careful postoperative monitoring is mandatory[2]. Jones et al.[10] reported recurrence times ranging from 1.5 months to 4 years. Therefore, the duration of follow-up should exceed 5 years if complete resection is not performed.

We opted for complete resection of the lesion, which occupied more than 2/3 of the nipple. This resulted in the excision of the entire nipple and part of the areola, yielding a 1.6 cm specimen with free margins. We also chose to perform immediate nipple reconstruction.

CONCLUSION

Nipple adenoma, also known as syringomatous cystadenoma, is a rare type of benign tumor that can occur on the skin or cutaneous appendages, such as sweat glands and sebaceous glands. Clinically, it mimics Paget's disease of the nipple or malignant breast lesions. Due to its rarity, nipple adenoma can easily be overlooked as a differential diagnosis in clinical practice.

The possibility of a syringomatous tumor should be considered when a patient presents with nipple discharge and erosion, with or without a palpable nodule beneath the nipple. This condition also presents a challenge for histological diagnosis. Accurate histological and immunohistochemical analysis is important to distinguish nipple adenoma from invasive carcinoma.

Due to the risk of recurrence, resection with clear margins should generally be recommended. In cases where resection results in compromised margins, follow-up may be required.

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal. This report was approved by the Ethics Committee under number 6.639.583.

AUTHORS' CONTRIBUTIONS

JLAA: Writing – original draft, Writing – review & editing, Supervision, Validation. UWS: Project administration, Resources, Software. MLMD: Formal analysis, Investigation, Funding acquisition. WP: Formal analysis, Conceptualization, Data curation, Investigation, Funding acquisition. DTSMN: Project administration, Formal analysis, Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Investigation, Methodology, Funding acquisition, Resources, Software, Supervision, Validation, Visualization.

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CASE REPORT
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The challenging diagnosis of granular cell tumor of the breast: a case report

Júlia de Faria e Azevedo Ramos[1]*, Guilherme Junqueira Souza[2], Alexandre Tafuri[3], Antônio Alexandre Lisbôa Ladeia[3], Carlos Alberto da Silva Ramos[3]

ABSTRACT

Conventional granular cell tumors, derived from Schwann cells, occur in soft tissues and are mostly benign. It is also recognized as Abrikossoff's tumor or granular cell myoblastoma, and the most common locations are found in the head, neck, arms, esophagus, and respiratory tract. The incidence in the breast is rare, representing only 8% of granular cell tumors. However, it is important to consider it as a differential diagnosis when investigating breast nodules due to its misleading presentation. This is a challenging diagnosis considering that the clinical examination and imaging workup may suggest signs of malignancy. Therefore, the lack of histopathological analysis may lead to erroneous conclusions and therapies. Due to non-specific imaging and physical examination findings, a biopsy of the lesion is mandatory for diagnosis. The tumor's microscopic criteria consist of the presence of large polygonal cells, with eosinophilic, granular, and abundant cytoplasm. The cell borders are indistinct and the growth pattern is infiltrative, with perineural and possible perivascular involvement; however, mitotic figures are rare. The present case report demonstrates the importance of anatomopathological analysis for this diagnosis. It refers to a female patient, 28 years old, complaining of a breast node. She was followed up in the Mastology Department for further investigation, with a mammography report identifying a speculated nodule, with undefined margins, classified as Bi-Rads 5 in the right breast, and an ultrasound reporting a Bi-Rads 4C solid nodule. The clarification was made through biopsy, which determined microscopy compatible with the rare tumor of granular cells in the breast, in addition to the immunohistochemical profile, which differentiated the tumor variant of non-neural origin, composed of ovoid cells with eosinophilic granules, presenting nuclear pleomorphism, atypia, and mitotic figures.

KEYWORDS: granular cell tumor; breast tumor; breast neoplasms; Schwann cells.

INTRODUCTION

Conventional granular cell tumors occur in soft tissues and are mostly benign[1]. It is also recognized as Abrikossoff's tumor or granular cell myoblastoma, whose most common locations are the head, neck, arms, esophagus, and respiratory tract[2,3]. The incidence in the breast is rare, representing only 8% of granular cell tumors[3]. However, it is important to consider it a differential diagnosis when investigating breast nodules due to its misleading presentation. After all, conventional granular cell tumors of the breast may mimic malignant tumors, both in clinical manifestation and in imaging examinations, leading to diagnostic errors and inadequate radical treatments[2].

On mammography, a granular cell tumor may reveal a solid nodule with spiculated or irregular margins, and on ultrasound, it may define a heterogeneous, vascularized nodule, with anisotropy and acoustic shadow, determining non-specific findings more associated with malignancy[1]. Therefore, as imaging tests do not exclude a malignant neoplasm, the differential diagnosis can be challenging and induce major psychosocial disorders in the patient. As a rule, definitive identification depends on the anatomopathological analysis of the lesion[4]. In macroscopy, it appears as an irregular and firm mass, with or without skin retraction and nipple inversion[3]. Microscopically, it is characterized by the composition of epithelioid cells with granular eosinophilic cytoplasm with abundant lysosomes[5].

[1]Faculdade Ciências Médicas de Minas Gerais – Belo Horizonte (MG), Brazil.
[2]Hospital Público Regional Prefeito Osvaldo Rezende Franco – Betim (MG), Brazil.
[3]Laboratório Tafuri de Patologia de Belo Horizonte – Belo Horizonte (MG), Brazil.
***Corresponding author:** juliaramos_@hotmail.com
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CASE REPORT

A 28-year-old female patient was admitted to the Mastology service at a regional hospital in Sete Lagoas, Minas Gerais, complaining of a nodule in her right breast, which she initially noticed six months ago. She claimed to be previously healthy, without comorbidities or allergies. Furthermore, she reported a history of two previous pregnancies, the last one in 2020 with breastfeeding for a year. Her menarche was at age 12, and she currently has regular cycles, using a copper intrauterine device (IUD) implant since 2021. Regarding her family history, she reported an aunt with ovarian cancer and two uncles with bowel cancer.

In a subsequent ultrasound examination, a breast imaging reporting & data system (Bi-Rads) 4C nodule was diagnosed, identifying a solid, hypoechoic, spiculated, non-circumscribed nodular image, with a posterior acoustic shadow, located in the retroareolar region of the right breast, measuring 1.8 x 1.9 x 1.3 cm. The mammogram, performed some months later, presented a poorly defined spiculated nodule in the right breast, with Bi-Rads 5 classification, and another nodule in the left breast with Bi-Rads 2 characteristics. Following the propaedeutic investigation, a guided core biopsy was performed using ultrasound. The result indicated a granular cell tumor.

A sectorectomy of the right breast was performed on the patient, with total resection of the tumor. The macroscopic examination revealed a firm, brown nodule measuring 2.5 x 2.4 cm, located 0.3 cm from the deep margin (Figure 1). The microscopy confirmed the diagnosis of neural granular cell tumor, with proliferation of polygonal cells, without atypia, with large and granular cytoplasm supported by dense, fibrous connective tissue, and no signs of malignancy (Figures 2 and 3).

An immunohistochemical study was requested, which demonstrated the panel: AE1AE3 antigen and AE1/AE3/PCK26 antibody negative; CD68 antigen and KP-1 antibody positive; negative GATA3 antigen and L50-823 antibody; negative P63 antigen and 4A4 antibody; and S100 antigen and positive polyclonal antibody.

The patient evolved in good general condition, without lymphadenopathy or phlogistic signs on post-operative examination. She was advised about the rarity of the condition and the need for follow-up with a new ultrasound in six months.

DISCUSSION

The conventional granular cell tumor, derived from Schwann cells, is most common in soft tissues, mainly found in the head, neck, arms, or chest wall. Its occurrence in the breast is rare, representing

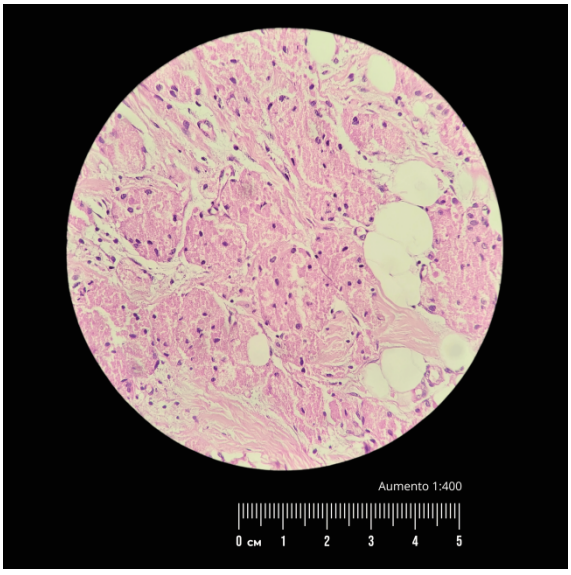

Figure 2. Microscopy of the lesion.

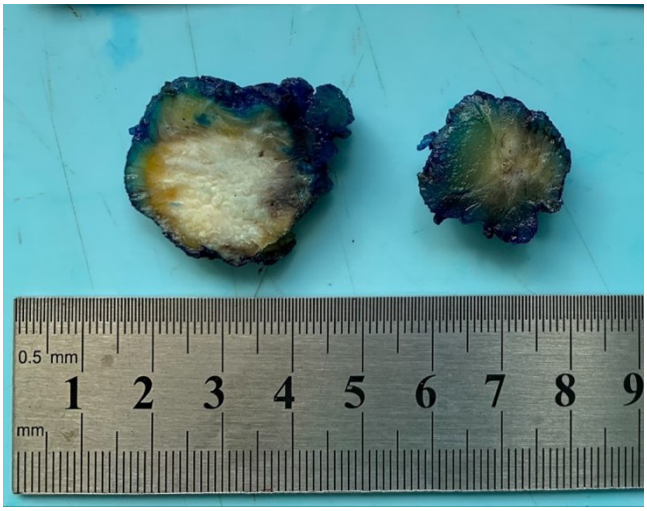

Figure 1. Macroscopy of the lesion.

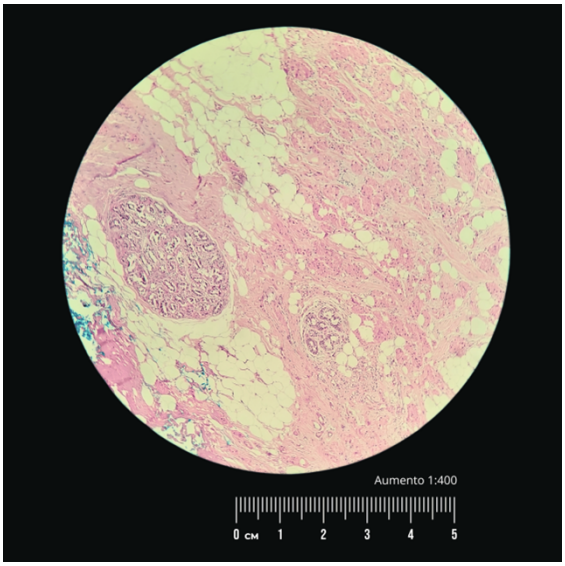

Figure 3. Microscopy of the lesion.

less than 10% of all granular cell tumors[5,6]. Considering tumors that affect the breast in general, granular cell tumors represent less than 0.1%[5,6]. Regarding the incidence in malignant form, it represents 1% to 2% of the category[1,3,5]. Epidemiologically, the tumor affects more women, across a wide age range from 19 to 77 years, and when it eventually affects men, it's more common in young adults of African descent[3].

Thus, granular cell tumors, which represent 1 in every 1,000 breast tumors, should be considered as a differential diagnosis for the investigation of breast nodules[3]. Mainly, because it is a challenging diagnosis considering that the clinical examination and imaging exams can suggest signs of malignancy, and the lack of histopathological analysis may lead to erroneous conclusions and therapies[2,5,7]. Therefore, due to non-specific imaging and physical examination findings, the lesion biopsy is mandatory for diagnosis[1,2].

The microscopic criteria of this tumor consist of the presence of polygonal large cells, with eosinophilic, granular, and abundant cytoplasm[3,5]. The cell borders are indistinct and the growth pattern is infiltrative, with perineural and perivascular possible involvement; however, mitotic figures are rare[3]. The present case obtained decisive histological confirmation with core biopsy analysis and the biopsy after the right breast sectorectomy. After all, the imaging tests were suggestive of malignancy, with a Bi-Rads 5 report mammography, and an ultrasound, with a Bi-Rads 4C result.

The variant of granular cell tumor of non-neural origin, unlike the conventional presentation, is composed of ovoid cells with eosinophilic granules, presenting nuclear pleomorphism, atypia, and mitotic figures, conferring a greater potential for lymphatic dissemination[8]. Immunohistochemistry is essential to determine a differential diagnosis, as the non-neural tumor is negative for S100 protein and other neural or melanocytic markers[9].

The immunohistochemical profile of conventional granular cell tumors shows positive for S100, CD68, CD63 (NKI/C3), and NSE, which may be related to cytoplasmic lysosomes reactivity, but the Ki-67 proliferation index is usually low[3]. As 10% of malignant cases are also positive for the S-100 marker, it is essential to search for other markers, such as CD68, which demonstrates lysosomal activity associated with the perineural Schwann cell[10]. In the reported case, we have a corresponding panel result, showing positivity for S100 and CD68.

The recommended treatment for the case is local surgical excision with free margins, without total mastectomy or sentinel lymph node biopsy, due to its mostly benign nature[2,3,10]. The prognosis for granular cell tumors of neural origin is good, and the recurrence rate is less than 10% after resection with appropriate margins[2,3,10]. The statistics regarding non-neural granular cell tumors are also positive, characterized by an indolent evolution, despite some worrying histopathological signs[9]. However, the malignant form can metastasize, including distant dissemination, which requires attention to worse prognostic characteristics of conventional granular cell tumors, such as a size greater than 5 cm, pleomorphism, prominent nucleoli, mitotic figures and necrosis[5].

CONCLUSIONS

The correct diagnosis of a conventional granular cell tumor of the breast is decisive for its psychosocial impact and for defining appropriate therapeutic management. It is a rare pathology, mostly benign, but challenging to diagnose. Due to non-specific imaging and physical examination findings, histopathological study is mandatory to rule out malignancy, along with immunohistochemical analysis of the lesion, which is important to differentiate from non-neural granular cell tumor.

AUTHORS' CONTRIBUTIONS

JFAR: Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. GJS: Conceptualization, Data curation, Investigation, Supervision, Visualization. AT: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – review & editing. AALL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – review & editing. CASR: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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CASE REPORT
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Breast lobular carcinoma metastatic to the cervix: case report

Julia Wolff Barretto[1]*, Maria Thereza Burko Rocha[2], Miguel Mazorra Coelho Vieira[2], Sérgio Ossamu Ioshii[2], Júlia Costa Linhares[2]

ABSTRACT

Breast cancer is the most common cancer among women, with 5 to 15% of these cases classified as invasive lobular carcinoma (ILC). Metastases can occur at any stage of the disease, with the most common sites being bones, lungs, lymph nodes, liver, and brain. However, extragenital metastasis to the uterus is rare. This study describes a case of a 52-year-old woman with breast pain for over a month. Mammography indicated a suspicious nodule (BIRADS 5). Physical examination revealed a breast nodule, *peau d'orange* skin, and axillary mass. Core biopsy diagnosed invasive lobular carcinoma. Tomographies suggested bone metastases. Additionally, she presented with abnormal uterine bleeding, and ultrasonography showed a suspicious uterine nodule, confirmed as a metastasis of ILC by immunohistochemical analysis. She had been treated with anastrozole since November 2023, with symptom reduction and clinical follow-up. It is known that ILC is the breast cancer most likely to metastasize to the genital tract. Previous reports mention difficulties in differentiation through imaging exams, with definitive differentiation achieved by biopsy of the cervix and/or later by surgery for tumor excision, with histopathological analysis and immunohistochemical profiling. There is limited scientific data on treatment options and prognosis in these cases. A study of approximately 1,650 patients with metastatic lobular carcinoma showed an overall survival of about 34 months. Thus, it is concluded that metastasis of invasive lobular carcinoma to the cervix is a rare entity, and this study aimed to contribute to the understanding of this condition and increase scientific evidence on the topic.

KEYWORDS: breast neoplasms; neoplasm metastasis; cervix uteri.

INTRODUCTION

Breast cancer is the most commonly diagnosed malignant disease in women (with an estimated 2.1 million new cases in 2018) and is the leading cause of cancer-related death in women in over 100 countries[1]. The National Cancer Institute (INCA) projects approximately 73,000 new cases in Brazil for the 2023–2025 triennium, with an adjusted incidence rate of 41.89 cases per 100,000 women. The age-adjusted mortality rate from breast cancer in women in Brazil, based on the world population, was 11.71 deaths per 100 women, with higher rates observed in the Southeast and South regions and a progressive increase with age[2].

Invasive lobular carcinoma accounts for 5 to 15% of all breast carcinomas. While the incidence rates of invasive ductal carcinoma have remained stable, those of lobular carcinoma have been steadily increasing since 1980. This rise presents a significant clinical challenge, as lobular carcinoma is more difficult to detect through both physical examination and mammography[3].

Metastases can occur in both early-stage and locally advanced breast cancer, with the most common sites of dissemination being the bones, lungs, lymph nodes, liver, and brain[4,5]. Metastases of extragenital origin to the uterus are rare, typically affecting the uterine body, while metastases to the uterine cervix represent an extremely rare site for this neoplasm[4,6,7].

Metastasis is the stage of cancer progression associated with the highest mortality, making knowledge of rare metastatic sites crucial for the early detection and interpretation of symptoms.

This study aims to report a case of lobular carcinoma in a 52-year-old female patient, presenting with metastases to the cervix and ovaries. Specifically, it focuses on a case of breast lobular carcinoma metastasizing to an exceptionally rare site, the cervix.

[1]Faculdade Pequeno Príncipe – Curtitiba (PR), Brazil.
[2]Hospital Erasto Gaertner – Curtitiba (PR), Brazil.
***Corresponding author:** juliaclinhares@yahoo.com.br
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CASE REPORT

A 52-year-old female patient, previously healthy and in her reproductive years, G2C2, with menarche at 14 years, was referred to Hospital Erasto Gaertner (HEG) in May 2023, presenting with breast pain, changes in skin appearance, and a palpable nodule in the right breast. Symptoms began one month prior to her referral to this facility. Mammography revealed diffuse increased breast density, nipple retraction, diffuse architectural distortion, extensive radiodensity in the middle third of the breast, an ill-defined radiodensity in the right axillary region, and a slightly lobulated nodule, approximately 9 mm, in the right axillary region. These findings were classified as BIRADS 5.

During her first consultation with a breast specialist in July, physical examination revealed a locally advanced tumor in the right breast. The skin displayed a *peau d'orange* appearance and thickening throughout the breast, with firmer areas in the upper quadrants and retroareolar region, as well as nipple and skin retraction in the inferolateral quadrant. Additionally, a palpable mass was detected in the ipsilateral axilla, suggestive of lymph node involvement. A core biopsy was performed, and staging tests were ordered.

Core biopsy identified invasive lobular carcinoma, with additional immunohistochemical studies showing positivity for hormone receptors (estrogen and progesterone), negativity for HER2, and a proliferative index (Ki67) of 5%. Staging via computed tomography scans revealed predominantly sclerotic oval lesions scattered throughout the skeleton, which are suspicious for metastatic disease.

In addition to the breast complaint, the patient reported abnormal uterine bleeding, specifically menometrorrhagia. A transvaginal ultrasound was performed (Figure 1), which showed an anteroverted uterus with smooth contours and a uniform myometrial texture, except for a well-defined, hypoechoic, heterogeneous nodular image on the posterior uterine wall, suggestive of an intramural myoma, measuring 19 x 18 x 20 mm. Uterine dimensions were increased, in addition to the reported parity (11.1 x 5.5 x 8.2 cm. Volume: 250 cm^3). The uterine cavity was patent, measuring 14 mm, with heterogeneous contents inside, and no flow detected on Doppler, which may indicate blood content. The ovaries were of normal dimensions for the age group, and no free fluid was observed in the pelvic fundus or tubal collections. The cervix appeared normal, measuring 4.3 cm in its longitudinal axis.

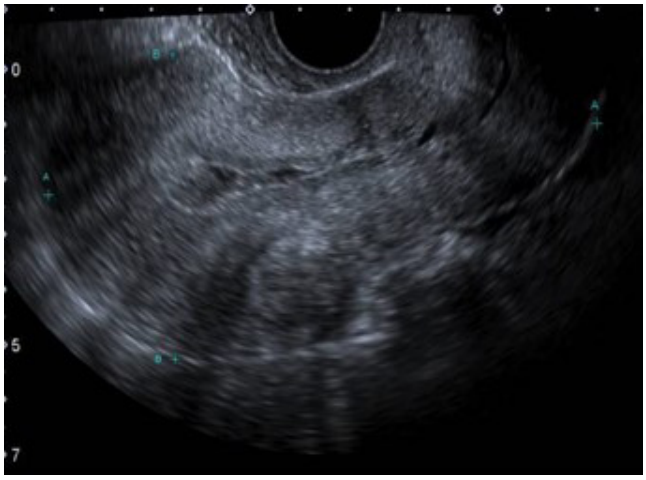

Figure 1. Transvaginal ultrasound showed increased uterine dimensions, along with the reported parity (11.1 x 5.5 x 8.2 cm. Volume: 250 cm^3), a patulous uterine cavity of 14 mm, and heterogeneous content within it. Source: the authors.

Hysteroscopy was conducted, and the curetted material was sent for histological analysis. The results revealed atypical cell proliferation in the endocervical stroma. Immunohistochemical analysis identified metastasis of lobular breast carcinoma (Figure 2), with positive hormone receptors and negativity for HER2 (Figure 3).

The patient underwent laparotomy for salpingo-oophorectomy, aimed at achieving castration, along with peritoneal biopsy and peritoneal lavage cytology. Histological analysis of these samples also confirmed metastases of lobular breast carcinoma, with immunohistochemical findings consistent with those previously observed (cervix and breast).

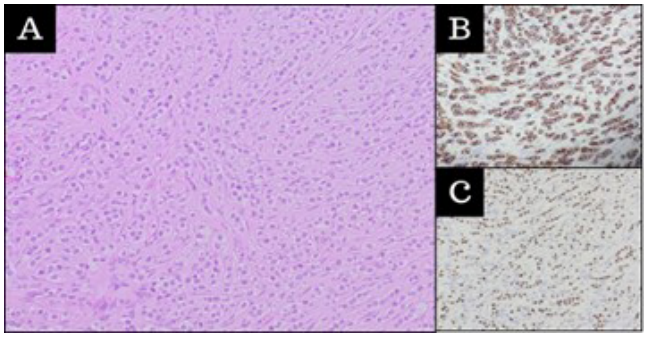

Figure 2. A: Neoplasia with cord-like distribution, featuring small cells with low nuclear grade (optical microscopy, hematoxylin and eosin, 400x); B: positivity for cytokeratin 7; and C: positivity for GATA3 (optical microscopy, immunohistochemistry, 200x).

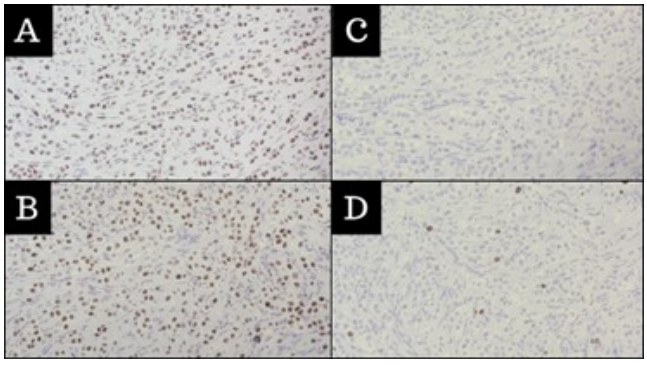

Figure 3. Immunohistochemical study showing positivity for hormonal receptors (estrogen (A) and progesterone (B)) and negativity for HER2 (C). The Ki67 proliferative index (D) was approximately 5% (optical microscopy, immunohistochemistry, 400x).

The patient is being monitored by professionals from the clinical oncology and mastology services; she developed anemia secondary to menometrorrhagia and is currently using ferrous sulfate, which has led to improvement in her hematimetric indices. For the treatment of breast neoplasia, anastrozole was prescribed and began in November 2023. The patient has tolerated the medication well, and during the last consultation (in December), she reported a significant reduction in right axillary lymph node enlargement, "softening" of the breast, and a decrease in right breast hyperemia.

DISCUSSION

Lobular carcinoma is the primary malignant breast neoplasm most commonly metastasizing to the genital tract, although extragenital metastases to the uterus are rarely observed[7].

Histologically, lobular carcinoma is characterized by cells with minimal cohesion, either embedded in fibrous tissue or arranged in linear cords. These cells have rounded or oval nuclei with a rim of cytoplasm. Typically, mitoses are absent[4,5].

Immunohistochemical studies are conducted to distinguish metastatic lobular carcinoma from primary cervical neoplasms[4]. The panel for metastatic lobular carcinoma typically shows positive CK-7 and negative CK-20, with the breast-specific marker GCDFP-15 also positive. Lobular carcinoma is usually characterized by a loss of the adhesion protein E-cadherin. However, approximately 15% of lobular carcinomas do not exhibit this loss of expression[4,5].

Breast and gastrointestinal tumors are the most common extragenital cancers that metastasize to the uterus, with lobular carcinoma being the most prevalent histopathological type to do so[6,7]. Uterine and vaginal metastases typically present with vaginal bleeding, while ovarian metastases often appear as asymptomatic ovarian masses[8].

The ovaries are the most common sites of metastasis within the female genital tract, due to their extensive vascularization and lymphatic drainage[9]. In contrast, the cervix has limited vascular supply and only an afferent lymphatic drainage system, which may account for the relative rarity of metastases to the cervix compared to the ovaries[6].

Lobular carcinomas exhibit a distinct pattern of metastasis distribution compared to non-special type carcinomas (ductal, not otherwise specified). They show a lower frequency of regional lymph node metastases and a higher incidence of metastases to distant sites, including the gastrointestinal tract, bones, skin, meninges, uterus, and ovaries[3].

The clinical characteristics of uterine involvement are often nonspecific, typically presenting as vaginal bleeding and abdominal discomfort[6]. Anatomopathological findings from a previously published study reporting a case of lobular carcinoma with metastasis to the cervix indicated that the metastasis appeared as a protruding mass with a whitish appearance on section, resembling the pattern found in leiomyomas[10].

Differentiating metastatic tumors from primary reproductive system tumors is essential for accurate staging and treatment, though it can be challenging. Previous reports highlight difficulties in distinguishing these tumors through imaging tests, with some cases of metastatic lobular carcinoma presenting as lesions that mimic leiomyomas[10].

Definitive differentiation can be achieved through cervical biopsy and/or post-surgical tumor removal, with histopathological analysis revealing the linear pattern characteristic of lobular carcinoma and an immunohistochemical profile consistent with this diagnosis[3,10,11].

Treatment options for cervical metastasis are influenced by individual factors such as the extent of the disease, the presence of other metastases, and the patient's performance status. Given the rarity of lobular carcinoma metastasizing to the cervix, there is limited well-established scientific data on treatment options and prognosis for these cases.

Previously published reports have documented the isolated use of adjuvant palliative therapy with anastrozole and S-1, as well as palliative chemotherapy with 5-fluorouracil, epirubicin, and cyclophosphamide, followed by hormone therapy. Additionally, the use of palliative radiotherapy for symptom management has been reported[10-12].

In a study involving approximately 1,650 patients with metastatic lobular carcinoma, the overall survival rate was approximately 34 months; there are no specific studies that address the survival of patients with this type of cancer metastasizing to the cervix[13].

CONCLUSIONS

Lobular carcinoma of the breast presents diagnostic and therapeutic challenges, particularly when it metastasizes to uncommon distant organs. This case report underscores the importance of meticulous clinical follow-up and interdisciplinary collaboration for the effective management of patients with this neoplasm and cervix metastases. Further studies are required to develop specific therapeutic approaches and enhance patient outcomes.

AUTHORS' CONTRIBUTION

JWB: writing – original draft, writing – review & editing. MTBR: data curation, investigation, writing – original draft, writing – review & editing. MMCV: data curation, investigation, writing – original draft, writing – review & editing. SOI: conceptualization. JCL: conceptualization, data curation, investigation, supervision, project administration, writing – original draft, writing – review & editing.

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On page 1 it was included:

José Guilherme Maia[2]

On page 5 it was included:

AUTHOR'S CONTRIBUTIONS

JGM: Data curation.