The importance of the study of breast neoplasms for the diagnosis: Case report

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ABSTRACT

Objective: This article aims to highlight the importance of the study of breast neoplasms and their importance for the diagnosis of this disease, regarding its epidemiology, etiology, clinical manifestations, diagnosis, screening and treatment. In addition, to deconstruct the stereotype that all patients with breast cancer present the same manifestations and evolve equally, in addition to reinforcing the understanding that each individual needs comprehensive care, so that not only the doctor, but the entire multidisciplinary team, can provide quality care, observing and respecting the specificities of each person, with the aim of offering - in addition to cancer treatment - quality of life.

Keywords: Breast cancer, Early diagnosis.

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INTRODUCTION

Worldwide, according to the WHO, breast cancer is the most prevalent cancer in women - Except for non-melanoma skin cancer. In addition, it also represents the cancer that leads to the highest mortality in this population. Despite the good clarification about genetic, hormonal and environmental risk factors, this pathology still faces many barriers in its screening and diagnosis.

In this context, it is known that the study of this pathology is extremely important and, from this perspective, the present work aims to carry out a literature review about the main characteristics of this disease and its importance today.

PRESENTATION OF THE CASE

The chosen case aims to explain the difficulties for the diagnosis of breast neoplasia, in addition to showing how a complete anamnesis and physical examination, together with well-analyzed complementary exams, are essential for the early detection of this disease. The case study was taken from the paper "Self-knowledge as an important factor in the diagnosis of breast cancer: a case study" by Guerra et al. (2020).

Patient CFL, 44 years old, married, teacher, born and coming from Cabeceiras-GO. She reported menarche at 14 years of age G2 P2 (n+c) A0, first child at 31 years of age and second at 35 years of age, having breastfed both children for 2 years, use of combined oral contraceptives since the age of 22 years, and during the lactation period of the first child she used a minipill and after the second delivery she underwent tubal ligation.

About 2 years ago, at the age of 42, she noticed a depression in her right nipple, without a palpable nodule, pain and papillary discharge. She went to the physician of the UBS in her municipality, who requested a mammogram (MMG). On her return, in September 2016, MMG had a BIRADS 2 finding (benign findings) and the professional advised her that it was possibly retained milk.

Not satisfied with the doctor's conduct, the patient reported that she sought a mastologist in another city, who requested MMG and breast ultrasonography (USGM). On follow-up, the MMG (which was performed in a different clinic than the first) showed a BIRADS 3 result (probably benign findings) and the USGM was within normal limits. In view of these findings, the mastologist agreed with the initial conduct of the UBS physician.

As time went by, the patient noticed that the nipple retraction was intensifying and decided to look for another doctor in her city in January 2017, who, after examining her and taking note of her clinical history, referred her to a hospital referral service. When she was seen at this service, in possession of a new MMG with BIRADS 3, the physician reported that the alterations were not worthy of concern, but upon examining her, he realized that the imaging findings were not

compatible with the clinical findings. Subsequently, the patient was taken to the mammography machine, and when another MMG was performed, no findings suggestive of malignancy were found. Faced with this, the doctor met with the team and they decided to change the compressor. When a new MMG was performed, alterations suggestive of malignancy were found (BIRADS 5).

The medical team requested a needle fragment biopsy (BFA) or core biopsy, which showed grade I lobular infiltrating breast carcinoma; in addition, he also requested: Scintigraphy, Chest Tomography, Pelvic and Abdomen USG, Oncoparasitic Cytology, Blood Count, AST, ALT; which had normal results, in addition to immunohistochemistry.

On the return visit, already in possession of the aforementioned tests, the team prescribed chemotherapy treatment with neoadjuvant intent. The patient underwent eight cycles of chemotherapy with an interval of 21 days, the first four cycles of Adriamycin and Cyclophosphamide and the last four of Paclitaxel, ending on March 1, 2018.

Weeks later, the patient developed pneumonia and was admitted for antibiotic therapy at the same referral hospital.

After resolution of the infection, a mastectomy was scheduled and performed on April 7, 2018. Currently, the patient is in good general condition, with no urinary and intestinal complaints, no alterations in the cardiovascular and respiratory systems, complaint of amenorrhea and pain in breast shock that does not cease with analgesics or opioids since the beginning of chemotherapy. The patient denies a history of cancer in the family and remains under follow-up at the oncology referral service.

DESCRIPTION OF THE HEALTH-DISEASE PROCESS

Breast cancer was mentioned in a medical papyrus by Edwin Smith in 1,600 B.C., however, its greatest clarification only happened in the twentieth century, mainly with the discovery of the x-ray and the development of chemotherapy in 1930. Mammography, the main radiological examination for the detection of breast cancer, was only introduced in 1960 and it was of great importance for early detection, which greatly helped to improve the survival of women diagnosed. From 1990 until today, awareness campaigns about this disease, such as Pink October, have been extremely important in order to bring social and political attention to this situation of such relevance in our country.

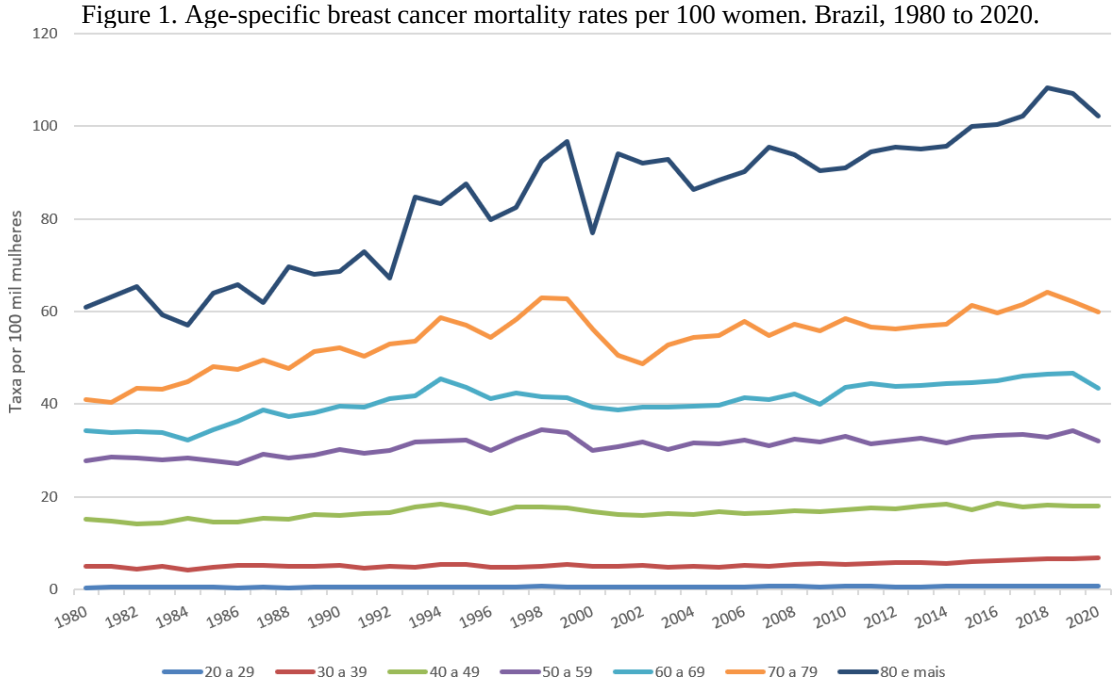
In Brazil, according to the National Cancer Institute (INCA), breast cancer is the most frequent type in women, as well as in the world, after non-melanoma skin cancer. Regarding mortality, this type is more prevalent, especially after the age of 40. Also according to INCA, it was predicted for the year 2023 that the incidence would be 41.89 cases per 100,000 women, that is, an estimate of 73,610 new cases diagnosed.

It is known that the number of cases in Brazil is not similar in the 5 regions of Brazil and the highest rates are in the South and Southeast regions. The northern region has a lower number, however, this region has a lower number of mammographs, which makes it possible to question this number, which may be low due to underdiagnosis and underreporting.

The incidence of this pathology increases according to the age of the patient, usually from the age of 50, and is rare in young women. It is important to note that trans men who have not undergone mastectomy continue to have the same risk and, therefore, should continue with screening and periodic visits to doctors in order to examine their breasts. Cis men are also affected, however, they represent only 1% of the cases of the disease and, therefore, will not be the focus of this study.

Regarding mortality, INCA data show a growing increase in recent decades. In 2022, the regions with the highest proportional mortality due to breast cancer were the Southeast (17.2%) and Midwest (16.8%) and the lowest was the North region (13.6%). In addition, mortality increases progressively according to the patient's age group, as we can see in the image below.

Figure 1. Age-specific breast cancer mortality rates per 100 women. Brazil, 1980 to 2020.



Source: Inca. Atlas of Cancer Mortality. Accessed on: May 19, 2023

From an etiological point of view, it is known that the risk factors are:

- Gender: For every 135 women affected, 1 man is affected. Although it is more prevalent in women, when it affects men, it is usually more aggressive and has a worse prognosis, since, as there is no screening, it is usually diagnosed at a more advanced stage;
- Age: The most prevalent age group is 50-69. In women over the age of 70, this risk decreases;
- Positive family history: patients who have 1st degree relatives affected by breast cancer

have a 4-6 times higher risk of developing this neoplasm;

- Ionizing radiation in the chest region: mainly in the breast region;
- Previous history of breast cancer: if a woman has had cancer in one breast, the risk of developing it in the other breast is 5x higher than a woman in the general population without a history of breast cancer;
  - Genetics: Mutation in the BRCA 1 and 2 gene: Main genetic risk factor because it increases the risk by 60 – 85%. It is worth noting that this mutation also confers a risk for ovarian cancer.
  - Syndromes: Li Fraumeni Sd., Cowden Sd., Peutz-jeghers Sd., Muir-Torre Sd., Ataxia-telangiectasia and CDH-1 (hereditary gastric cancer sd.).
- Proliferative breast diseases: hyperplasia without atypia, papillomas, and sclerosing adenosis can increase the risk of breast cancer by 1-2x. Ductal hyperplasia and atypical lobular hyperplasia increase the risk of breast cancer by 5x. In addition, DCIS (ductal carcinoma in situ) and LCIS (lobular carcinoma in situ) are localized types of breast cancer, but they increase the risk of developing a new lesion by 10 times, compared to the normal population;
- Nulliparity: increases the risk by 30%;
- History of ovarian or endometrial cancer: increases risk by 2x;
- Early menarche (before 12 years of age);
- Late menopause (over 55 years of age): hormonal stimulation for a long period of life;
- Obesity: obese women produce estrone in peripheral fat, leading to an increase in circulating hormone rates;
- Alcoholism;
- Smoking;
- Lack of lactation;
- HRT (hormone replacement therapy): greater than or equal to 5 years ago.

On the other hand, there are protective factors against breast cancer:

- Regular physical activity: Studies show that women who have had breast cancer and practice regular physical activity after treatment have a decreased risk of recurrences, in addition to fighting obesity.
- Vitamins A and C
- Selenium
- Phytoestrogens (soy)
- Lactation

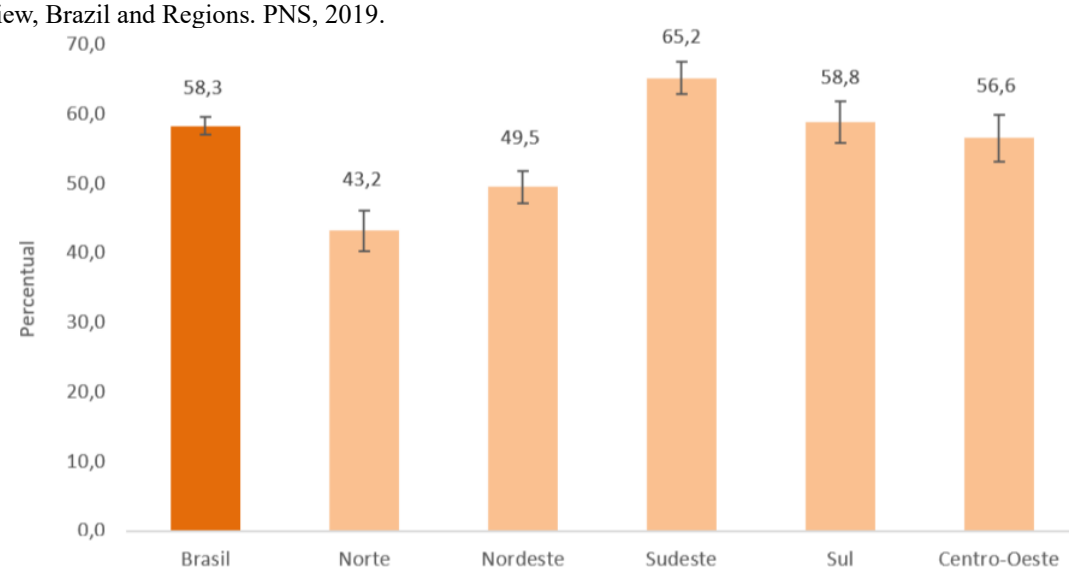
- Oophorectomy before the age of 35 years

From the etiological analysis, we can conclude that the genesis of breast cancer is multifactorial and that many individual and environmental factors may contribute to its formation. Breast neoplasms of the hereditary type, that is, related to mutations in the BRCA 1, BRCA2 and p53 genes, mainly, are equivalent to about 5-10% of the causes. In any case, the carcinogenesis of this neoplasm depends on genetic lesions in the DNA, through the activation of proto-oncogenes or inhibition of tumor suppressor genes, so that it can promote phenotypic changes in normal tissue and, consequently, evolve with breast neoplasia.

The diagnosis consists of two aspects, screening, which is an examination performed periodically (every 2 years) in cis women and trans men (who have not undergone mastectomy) within the age group of 50 to 69 years, and elective research done in patients with signs and symptoms that suggest carcinoma, such as nipple retraction, nodule and others. There are still no conclusive studies on the research on trans women, despite their greater hormonal exposure, however, they are not yet included in population screening as well as cis men.

Population screening is done through mammography and, in recent years, has received greater public investment. However, there is still some limitation because access to health services occurs mainly in the capitals and does not reach more distant populations. According to PNS data (IBGE, 2019), in 2019 only 58.3% of women had a mammogram less than two years ago, however, there was a divergence between women living in urban (60.5%) and rural (41.6%) areas. The women who have the highest access are those living in the South and Southeast regions, while the North and Northeast regions have the lowest percentages.

Figure 2: Proportion of women aged 50 to 69 years who underwent mammography less than two years before the date of the interview, Brazil and Regions. PNS, 2019.



Source: IBGE, Directorate of Research, Coordination of Work and Income, National Health Survey, 2019.

In addition, socioeconomic factors are also directly related to mammography. Patients with higher levels of education are related to higher screening, while those with no schooling or incomplete primary education are the ones who are less examined. In this same context, it was observed that the higher the financial income, the higher the screening rate in the last two years. Finally, in the period of the COVID-19 Pandemic, especially in 2020 and 2021, there was a significant drop in this process, but the proportion of women is expected to increase in the coming years.

Anamnesis and physical examination are part of the gynecological examination, and it is extremely important to collect a detailed history of the patient in order to identify possible risk factors, signs and symptoms associated with breast cancer. Self-examination is very indicated in order for the patient to know how to investigate alterations, however, it has limitations, mainly related to the correct technique. Therefore, it is important that the physical examination of the breasts is done by the physician in a systematic way through static and dynamic inspection and palpation. The static inspection aims to observe volume, shape, presence of bulges, retractions and lesions and the dynamic inspection performs maneuvers to identify changes in other positions. Palpation should examine the entire breast, including axillary and supraclavicular lymph nodes, and is primarily aimed at looking for masses. In addition, papillary expression should be performed when there is a complaint of papillary discharge.

Women with breast cancer usually have more local, rather than systemic, signs and symptoms. Among these, we can observe a change in the size or shape of the breast, pain in the breast and/or axillary region, presence of a mass in the breast and/or axillary region, change in skin thickening, nipple retraction, flushing, papillary discharge, lesions and eruptions around the nipple and/or on the skin, roughness (similar to orange peel) and/or undulations in the skin, and edema (irregular). When it is unilateral, it is usually more related to breast carcinoma.

Figure 3. Breast changes that can be seen in breast cancer: edema, nipple retraction, and "orange peel" appearance.

Source: http://www.radioinmama.com.br/tiposdemama.html

It is important to note that not every type of papillary discharge is associated with this disease and the most common changes related to it are crystalline or bloody discharge, especially when unilateral and spontaneous. This fluid must undergo cytological examination that can search for and identify cancer cells. Biopsy of the affected sinus may also be investigated, depending on the case.

In the office, the main complaint of patients is breast pain, followed by a palpable mass, and this information should be very well considered, together with the rest of the anamnesis and complementary exams. Pain, despite being the main complaint, is usually associated with benign changes, such as premenstrual period, trauma, neuritis, inflammation, and stress. In the same way, most of the nodules in the breast are benign cysts and adenomas, so the doctor should always communicate to his patient so that she does not develop great anxiety with one of the findings mentioned above.

In addition, despite having more local symptoms, cancer patients usually have comorbidities and are immunosuppressed, and therefore have infections and are hospitalized more frequently. These conditions can lead to other extramammary symptoms, such as pleural effusion, neutropenia, hemorrhagic diathesis, and others, especially when there is metastasis.

In Brazil, breast cancer screening is opportunistic, i.e., MMG is offered to asymptomatic women in the age group of 50 to 69 years at biennial intervals. However, as previously mentioned, the offer of this tool does not occur equally to the entire population in need. On the other hand, women at increased risk, who have a family history of a first-degree relative before the age of 50 or cancer in both breasts or ovarian cancer in any age group, a family history of male breast cancer, and a histopathological diagnosis of proliferative breast lesion with atypia or lobular neoplasia *in situ*,

should have an individualized clinical follow-up.

The diagnosis of breast cancer is based on clinical clinical studies associated with imaging tests and confirmed through histopathological evaluation. According to the findings, the best conduct to be adopted is defined. For early detection, the main test to be performed is mammography, in view of its high specificity and sensitivity in the identification of this pathology.

Mammography consists of a breast X-ray performed in a specific X-ray machine and in it it is possible to observe even the smallest lesions that appear in the initial phase of the disease. Radiological signs indicating malignancy are classified into direct and indirect. Direct signs consist of: nodules, microcalcifications, and asymmetric densities, both focal and diffuse. Indirect distortions are: parenchymal distortions, isolated ductal dilation, skin thickening, axillary lymphadenopathy, and retraction of the nipple-areolar complex and/or the skin.

As for nodules, those with a high density and spiculated contour are characterized by a high probability of being cancer. Regarding microcalcifications, which are defined as opaque particles measuring less than 0.5 mm, they may represent the earliest sign of malignancy, but only 20 - 30% are present in malignant lesions and to suspect cancer they must be in large quantities (> 5 per cubic centimeter), with different shapes (lines, branches, dots) and varied density within each one or between the particles. In addition, the distribution of microcalcifications is usually unilateral and may be present in a clustered manner over a small area or following a ductal path.

Self-examination can also be a tool that enables the early identification of malignant neoplasms, as the individual himself may find changes in the breast. However, the Ministry of Health does not present a recommendation to perform the self-examination. The main arguments against performing it are: unnecessary interventions due to false-positive diagnoses and the occurrence of non-palpable lesions that are not detected in this examination, which may influence the patient not to seek medical care.

The physical examination performed by a clinician is an accessible resource for the diagnosis of breast cancer, however, as well as the self-examination, it has limitations, and can negatively influence the patient's prognosis due to the diagnosis of false-positives or false-negatives, resulting in inadequate interventions or failure to perform the appropriate therapeutic approach. However, it is important for the recognition of some specific types.

Regarding complementary exams, it is known that ultrasonography is a complementary tool, being generally performed in people with higher breast density and/or under 40 years of age.

Magnetic resonance imaging has higher sensitivity than mammography, but it has variable specificity, in addition to having a high cost, making it recommended as a complementary test generally only for patients with high genetic risk. Given its high sensitivity, it is possible to identify initial lesions, multifocal tumors, and additional lesions not detectable in other methods.

For the standardization of the description, analysis of mammography and management, *the Breast Imaging Reporting and Data System* (BI-RADS) is the classification system adopted in Brazil according to the Brazilian Society of Mastology and the Brazilian Federation of Gynecology and Obstetrics, which analyzes parameters such as: grouping and morphology of microcalcifications, nodules and breast density. BI-RADS classifies breast lesions from 0 to 6:

- BI-RADS 0 - Inconclusive findings, need additional imaging or additional tests.
- BI-RADS 1 - No abnormalities, negative test. In this case, there are no significant abnormalities to be reported, the breasts are symmetrical, and suspicious masses, distorted structures, and/or calcifications are not present.
- BI-RADS 2 - Benign changes. The findings are benign such as benign calcifications and calcified fibroadenomas.
- BI-RADS 3 - Probably benign changes. With ≤ 2% risk of malignancy.
- BI-RADS 4 - Suspicious alterations, as they do not present the classic appearance of malignancy, but are doubtful to the point of justifying the request for biopsy.
    - 4A. Low suspicion of malignancy. With >2% to ≤10% risk of malignancy. The breast may contain palpable solid masses and/or partially circumscribed margins.
    - 4B. Intermediate suspicion of malignancy. With a risk of malignancy >10% to ≤50%. Masses with imprecise margins and with some circumscribed regions.
    - 4C. Suggestive of malignancy. With > 50% to < 95% risk of malignancy. It may present with ill-defined, irregular masses or clusters of pleomorphic calcifications.
- BI-RADS 5 - Highly suspicious change. With ≥ 95% risk of malignancy.
- BI-RADS 6 - Malignancy present, already confirmed.

According to the BI-RADS classification, the most appropriate conduct is:

- BI-RADS 1 - The exam must be repeated annually or biannually.
- BI-RADS 2 - The exam must be repeated annually or biannually.
- BI-RADS 3 - Follow-up should occur between 4 to 6 months. After that, it should be performed regularly for at least 2 years.
- BI-RADS 4 - Biopsy required for diagnostic confirmation. BI-RADS 5 - Biopsy required for diagnostic confirmation.
- BI-RADS 6 - Initiate treatment.

Breast cancer is also histologically classified into 3 grades according to the score obtained:

- Grade 1 or well-differentiated (given a score of 3, 4, or 5): Cancer cells are growing more slowly and are more similar to normal breast tissue.
- Grade 2 or moderately differentiated (score 6 or 7): cells have characteristics between grades 1 and 3.

- Grade 3 or poorly differentiated (score 8 or 9): the cells do not have characteristics similar to those of normal tissue and have a tendency to grow and spread aggressively.

There are also outpatient procedures that can also aid in the diagnosis, such as fine needle aspiration (cytological examination) and core needle puncture (histopathological examination).

After biopsy or surgical removal, the breast tissue is also submitted to an immunohistochemistry test (IHC) and classified as to the presence or absence of estrogen or progesterone receptors, which is also important for the best decision about the therapeutic approach. There are some receptors and neoplastic cells can contain one, both or none of them, so they are classified into: estrogen receptor positive (ER+), progesterone receptor positive (PR+), hormone receptor positive (HR+) when it has both receptors or hormone receptor negative (HR-) when it does not have any of the receptors.

In addition, some tumors have high levels of HER2 protein, being termed as HER2+ breast cancers that tend to grow and spread faster than other types. In this case, the sample obtained in the biopsy or surgery can be analyzed by means of IHC or fluorescent in situ hybridization (FISH), but the latter has a high cost and a long wait for the result, making the IHC the first to be requested.

The staging system for breast cancer is that of the American Joint Committee on Cancer (AJCC) which uses clinical and pathological parameters: the pathological (or surgical) is determined through the analysis of the tissue obtained in the surgery and the clinical (which is used when surgery is not possible) is based on physical examination findings, imaging and biopsy tests. However, in disseminated diseases, staging using only clinical criteria is less accurate than pathological staging to define the prognosis. In both forms of staging, 7 main criteria are used: T - size of the primary tumor and spread or not to other areas, N - spread to regional lymph nodes, M - presence of metastasis to other organs, ER - tumor contains estrogen receptor, PR - tumor contains progesterone receptor, HER2 - tumor contains HER2 protein and G - cancer grade, which indicates how much cancer cells resemble normal cells.

Regarding TNM staging, we have to:

- Primary tumor (T):
  - TX - The primary tumor cannot be evaluated.
  - T0 - No evidence of primary tumor.
  - Tis - Carcinoma in situ.
  - T1 - The tumor is up to 2 cm in diameter.
  - T2 - The tumor is between 2 cm and 5 cm in diameter.
  - T3 - The tumor is more than 5 cm in diameter.
  - T4 (includes T4a, T4b, T4c, and T4d) - Tumor of any size that invades the chest or skin.
- Regional lymph nodes (N):

- NX - Lymph nodes cannot be evaluated.
- N0 - Adjacent lymph nodes are free.
  - N0 (i+) - The area of disease spread contains less than 200 cells and is less than 0.2 mm.
  - N0 (mol+) - Cancer cells cannot be seen in the lymph nodes of the armpits, but traces of them have been detected using the RT-PCR technique.
- N 1 - Tumor spread has occurred to 1 or 3 axillary lymph nodes and/or internal mammary lymph nodes.
  - N1mi - Micrometastases in the lymph nodes under the upper limb with areas of tumor spread of 2 mm or less.
  - N1a - Spread has occurred to 1 to 3 lymph nodes in the arm with at least one area of disseminated disease greater than 2 mm in diameter.
  - N1b - Tumor spread occurred to the internal mammary lymph nodes. It is only possible to diagnose by sentinel lymph node biopsy.
  - N1c. N1a and N1b apply.
- N2 - The tumor has spread to 4 or 9 axillary lymph nodes or to the internal mammary lymph nodes.
  - N2a - Spread to 4 to 9 axillary lymph nodes with at least an area larger than 2 mm.
  - N2b - Spread to 1 or more internal mammary lymph nodes, increasing their size.
- N3 - Any of the following:
  - N3a - Spread to 10 or more axillary lymph nodes, with at least one area of disseminated cancer greater than 2 mm. Or, spread to infraclavicular lymph nodes with at least one area of cancer larger than 2mm.
  - N3b - Tumor present in at least one axillary lymph node with at least one area of cancer spread greater than 2 mm and enlarged internal mammary lymph nodes. Or, tumor with spread to 4 or more axillary lymph nodes with at least one area of spread greater than 2 mm and small amounts of tumor cells are found in the internal mammary lymph nodes on sentinel lymph node biopsy.
  - N3c - Spread to the clavicular lymph nodes, with at least an area larger than 2 mm.

- Distant metastasis (M)
  - MX - Dissemination cannot be evaluated
  - M0 - Absence of distant metastases.
  - cM0 (i+) - Small amounts of cancer cells found in the blood or bone marrow or small areas of cancer spread (less than 0.2 mm) found in lymph nodes, collarbones, or breast areas.
- M1 - Presence of distant metastases.

The treatment of breast cancer can be divided into pharmacological and non-pharmacological - and the therapeutic choice is influenced by the characteristics of the lesion, staging and specificities related to the patient.

PHARMACOLOGICAL TREATMENT

Pharmacological treatment is based on chemotherapy and hormone therapy, which can be implemented at different times of the disease.

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy (i.e., performed before surgical approach to the lesion) is indicated in the following settings:

- Treatment of locally advanced disease (T4, inflammatory, N2, N3).
- Relatively large operable tumors (T3).
- For patients who want conservative surgery, however, the relationship between breast size and tumor size is unfavorable.
- Patients with a clinically compromised axilla but an operable tumor, who may benefit from axillary downstaging.

Patients with tumors whose surgical approach is possible and with biological characteristics that favor the indication of chemotherapy (e.g., triple negative, HER2+, luminal B).

Neoadjuvant chemotherapy is a therapeutic measure that is closely associated with an increase in the rate of conservative surgeries due to its ability to reduce the size of tumor lesions - depending on the histological type of the lesion. However, its performance may have a negative impact on sentinel lymph node testing at the time of surgery because it results in lower rates of lymph node identification and a higher rate of false negatives when compared to patients who underwent a surgical procedure not preceded by chemotherapy.

Despite the disadvantages linked to side effects - such as pain, hair loss, malaise, nausea, vomiting, edema, nail weakness, hematological disorders, among others - studies show that neoadjuvant chemotherapy can reduce the recurrence rate of the disease and the mortality rate, being a therapeutic tool of great value for breast cancer patients who fit the pre-established indications.

Figure 4. Adjuvant/neoadjuvant chemotherapy protocols.

TABELA 3: Protocolos de Quimioterapia Adjuvante/neoadjuvante

Droga	Dose	Intervalo
PROTOCOLO AC_{dd}*-T (HER 2 negativo)		
Doxorrubicina	60 mg/m2,IV	A cada 14 dias x 4 ciclos
Ciclofosfamida	600 mg/m2,IV	
Paclitaxel	80 mg/m2,IV	Semanal x 12 semanas OU
Docetaxel	100 mg/m2,IV	A cada 21 dias x 4 ciclos

Droga	Dose	Intervalo
PROTOCOLO TC (HER 2 negativo)		
Docetaxel	100 mg/m2,IV	A cada 21 dias x 4 ciclos
Ciclofosfamida	600 mg/m2,IV	
Droga	Dose	Intervalo
PROTOCOLO AC*-TH		
Doxorrubicina	60 mg/m2,IV	A cada 14 dias x 4 ciclos
Ciclofosfamida	600 mg/m2,IV	
Docetaxel	75 mg/m²,IV	A cada 14 dias por 4 ciclos
Trastuzumabe	6 mg/kg - dosede ataque 8mg/kg,IV	A cada 21 diaspor 1 ano
PROTOCOLO: TCH adjuvante*(HER 2 positivo)		
Docetaxel	75 mg/m²,IV	A cada 21 dias
Carboplatina	AUC** 6,IV	Por 6 ciclos
Trastuzumabe	6 mg/kg -dosede ataque de 8 mg/kg,IV	A cada 21 dias por 1 ano
PROTOCOLO: **TH** adjuvante(HER 2 positivo)		
Paclitaxel	80 mg/m²,IV	Semanal por 12 semanas
Trastuzumabe	6 mg/kg- dose de ataque de 8mg/kg,IV	A cada 21 dias por 1 ano

Source: Permanent Commission on Health Care Protocols of the SES-DF, 2021.

Adjuvant chemotherapy

Adjuvant chemotherapy treatment (i.e., performed after surgery) should be considered according to some aspects, such as the subtype of breast cancer and the risk of recurrence.

The indicated subtypes are: hormone receptor-positive tumors (Luminals A and B), HER-2 positive tumors, and triple-negative tumors. These indications are based on the number of recurrences after surgical treatment of the lesion, for example, it is known that late recurrences (5 years later) are commonly seen in HER2-negative patients and in patients with luminal tumors. Situations in which adjuvant chemotherapy is not indicated:

- Hormone receptor-positive (RH+) tumor up to 1 cm and lymph node negative. (in these cases, adjuvant hormone therapy is indicated)
- Triple-negative tumor < 5mm.

Situations in which adjuvant chemotherapy is indicated:

- Tumor HER 2 positivo >T1b.
- RH+ tumor larger than 1 cm with histological grade 2/3 or positive lymph node.
- Triple-negative tumor larger than 6 mm.
- 0.6 to 1 cm RH+ tumor: Patients younger than 40 years, Grade III, with angiolymphatic

and perineural invasion present.

- Tumor with negative lymph node, RH+ > 1 cm, grade 1/2 or triple negative < 1 cm.

In addition to the indication of adjuvant treatment due to the characteristics related to the tumor lesion, there is an indication of adjuvant treatment due to risk stratification:

- Baixo risco: hormoniotherapy
- Intermediate-risk: DOCETAXEL + CYCLOPHOSPHAMIDE.
- High risco: AC (doxorubicin + cyclophosphamide) x 04 cycles followed by weekly paclitaxel x 12 cycles.

Figure 5. Risk stratification. Source: European Society for Medical Oncology/ESMO, 2015.

Alto Risco	Baixo risco
Mulheres Jovens (<40 anos)	Pós Menopausa
Grau Histológico III	Grau histológico I
HER2 positivo ou triplo negativo	Receptor hormonal positivo
Linfonodo positivo	Linfonodo Negativo
Invasão angio-linfática ou peri-neural presente.	Ausência de invasão de angio-linfática ou peri-neural.

Despite differing evidence in several studies, adjuvant chemotherapy should be started less than 12 weeks after surgery. The use of trastuzumab - a monoclonal antibody that can be used in both adjuvant and neoadjuvant - should be discontinued in patients who present with symptoms of heart failure and evidence of decreased ejection fraction until normal cardiac function returns, if this does not occur, it should not be restarted. If the interruption of use is equal to or greater than six weeks, for cardiological reasons or not, the initial dose may be repeated.

With regard to elderly patients, adjuvant chemotherapy should be performed considering ideal regimens and dosages - given that, in these patients, clearance and excretion may present some degree of impairment. In the case of obese patients, the recommended doses with actual body surface area should be followed so that the dosage administered can produce the desired therapeutic effect. Anthracicyclic studies show that there is no higher incidence of febrile neutropenia or higher mortality.

Despite the very low incidence, pregnant patients with malignant neoplastic lesions of the breast should be considered, since their treatment has a series of specifications, restrictions and contraindications. Surgical treatment is the main therapeutic measure, and adjuvant chemotherapy is

contraindicated in the first trimester of pregnancy - due to the higher risk of congenital anomalies, chromosomal abnormalities, stillbirth and abortion, with an estimated risk of fetal malformation during exposure in the first trimester of 15% to 20%. The dose of adjuvant chemotherapy in the pregnant woman should follow the body surface area throughout the treatment. In addition, according to data in the literature, the use of chemotherapy drugs during the second or third trimester was also associated with a series of complications such as: intrauterine growth restriction, prematurity and low birth weight in about half of the exposed children. The use of the drug methotrexate should be avoided throughout pregnancy due to its teratogenic potential and its important abortifacient effect. Regarding breastfeeding, it should be avoided in women using chemotherapy, with or without trastuzumab, and hormone therapy.

Palliative chemotherapy

Palliative chemotherapy is a therapeutic option for patients with advanced and/or metastatic disease - either lymphatic, blood, or direct extension. The median survival of a patient with metastatic disease is approximately two years, but it can vary, depending on the location of the metastases, from a few months to many years - this difference can be justified by the heterogeneity of breast cancer, however, there are no randomized studies in the literature that prove an increase in overall survival in palliative treatment, after the use of two chemotherapy lines or two hormone lines. The main chemotherapy drugs used are:

- First line: Tamoxifen
- Second line: Aromatase inhibitors
- Third Row: Fulvestrant
- Other drugs used in patients with advanced stages: anthracyclics (doxorubicin or epirubicin) and taxanes (paclitaxel, docetaxel), and other chemotherapeutic agents capecitabine, gemcitabine, methotrexate, fluorouracil, vinorelbine, vinblastine, mitomycin, cyclophosphamide, cisplatin, irinotecan, among others.

Palliative treatment follows protocols that may indicate different numbers of chemotherapy cycles, which will have toxicity and tolerance to treatment as the main limiting factors. However, there are no data in the literature that guarantee an ideal number of chemotherapy cycles to be used. In patients with rapidly progressing disease who require a rapid therapeutic response, multidrug therapy can be used, i.e., the use of several chemotherapy drugs simultaneously.

It is important to emphasize that the palliative treatment of breast cancer is not restricted to chemotherapy and may vary depending on numerous issues intrinsic to the patient (age, comorbidities, tolerance to side effects, among others), the lesion and the progression of the disease. The participation of a well-aligned multidisciplinary team with a comprehensive perspective of the

patient is essential for the success of palliation.

Hormonal therapy

Hormone therapy can be implemented in patients who do not meet the requirements for the administration of chemotherapy drugs - for example, postmenopausal patients, those with locally advanced tumors, hormone receptor-positive, and HER-2 negative. In addition, hormone therapy is also a treatment option for palliative patients, especially in patients with advanced, metastatic, receptor-positive and/or relapsed disease.

NON-PHARMACOLOGICAL TREATMENT

Radiotherapy

Radiotherapy (RT) can be used in different stages of the disease - adjuvant, palliative or neoadjuvant - and is an important non-pharmacological therapeutic tool for breast cancer patients.

Adjuvant radiotherapy

In view of the EBCTCG (Early Breast Cancer Trialists' Collaborative Group) meta-analysis - which evaluated the benefits of RT after conservative surgery and demonstrated that radiotherapy decreases the risk of recurrence of systemic or locoregional disease in 10 years from 35 to 19.3% - adjuvant RT is indicated for all patients undergoing conservative surgery - also called segmentectomy.

In addition to segmentectomy, other indications for RT in breast cancer patients are:

- Patients with four or more positive lymph nodes;
- Patients with a positive margin, when a new surgical intervention is not possible;
- Patients with tumor lesions greater than or equal to 5 cm.

NOTE: In patients with less than four positive lymph nodes, the risk-benefit of implementing RT should be carefully analyzed.

Paliative radiotherapy

RT can also be inserted in the context of palliative care in cases where there is: bone metastasis, intractable bone pain, brain metastasis, neoplastic spinal cord compression syndrome, intracranial hypertension, or bleeding.

Neoadjuvant radiotherapy

In contexts in which there has been therapeutic failure in neoadjuvant chemotherapy or hormone therapy, RT may be a treatment option for patients who will subsequently undergo surgical

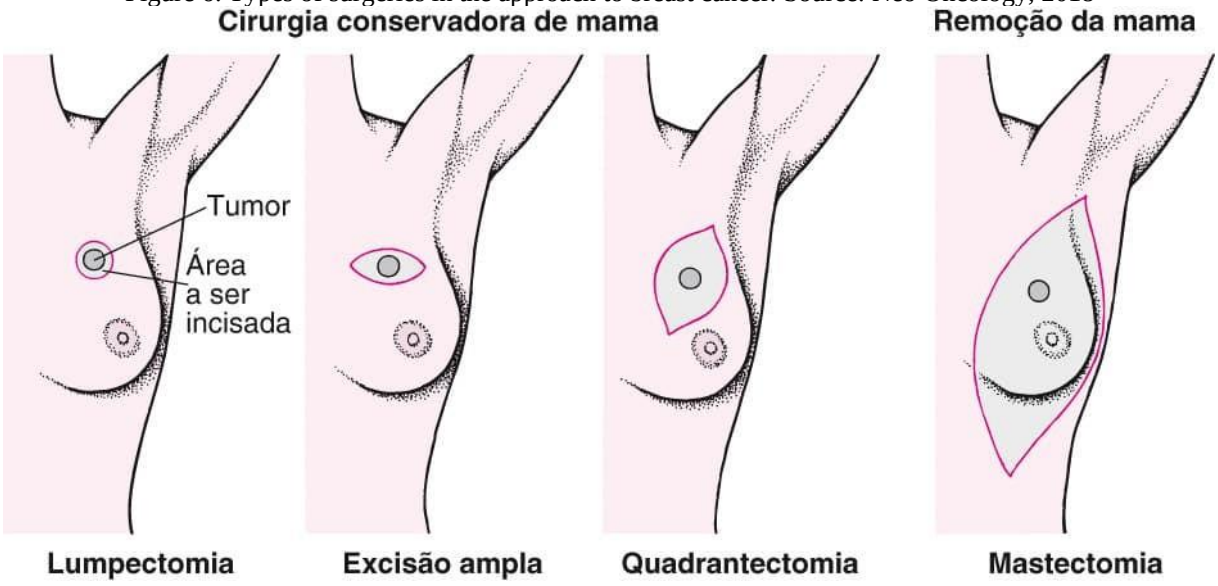
treatment.

SURGICAL TREATMENT: MASTECTOMY MAY BE THE ONLY OPTION, BUT IT CAN ALSO BE PERFORMED PROPHYLACTICALLY.

Conservative surgery, also called lumpectomy or partial mastectomy, is considered standard treatment for early-stage cases and should usually be combined with adjuvant radiation therapy. When compared to radical mastectomy, it has a similar survival rate, in addition to offering better aesthetic results and quality of life to the patient. For the indication, some criteria are used, such as tumor location and extent, size of the breast tissue, previous radiotherapy, and age of the patient, among others. Contraindications to lumpectomy are: inability to obtain negative margins, contraindications to radiotherapy, multicenter cancer in which excision of only a single region of breast tissue cannot occur with satisfactory aesthetic results, suspicious calcifications found diffusely in the breasts, some collagen vascular diseases, and previous radiotherapy to the breast involved in the surgery. In patients with more than three positive axillary lymph nodes in sentinel lymph node investigation, age < 50 years, and other factors associated with breast cancer recurrence, they should undergo radiotherapy after partial mastectomy. Radiotherapy can even be performed during surgery with a shorter exposure time, direct irradiation to the tumor bed, and a lower risk of injury to the circumscribed tissue.

Currently, sentinel lymph node biopsy (SLNB) is a less invasive technique with lower morbidity than radical lymphadenectomy. In cases where SLNB is negative, total dissection of axillary lymph nodes is not indicated, which avoids the occurrence of complications such as numbness of the affected limb and axillary network syndrome, for example. When up to 2 BLS are positive, axillary dissection is not necessary. When more than 3 lymph nodes are affected, total dissection should be performed.

Figure 6. Types of surgeries in the approach to breast cancer. Source: Neo Oncology, 2018



IMPORTANT ASPECTS ABOUT BREAST CANCER TREATMENT:

Monitoring

Patients undergoing palliative treatment should be constantly monitored, clinically and laboratory, so that it is possible to make dosage adjustment or change of antineoplastic drugs, when necessary.

Post-treatment follow-up

Patients undergoing adjuvant treatment should be followed up for at least 5 years after the end of treatment, with periodic physical examination of the patient (initially every 3 months and then annually) and post-treatment mammography for women who underwent segmentectomy (one year after the initial mammogram and 6 months after completion of radiotherapy). In addition, the use of laboratory tests (complete blood count, serum biochemical dosages), imaging (bone scintigraphy, chest X-ray, abdominal US, CT, MRI, PET-CT) is recommended only for symptomatic patients or in whom specific findings are evidenced in the clinical examination. Regarding patients with metastatic disease, follow-up is done by means of imaging tests at the affected sites every 3 to 6 months or in the event of signs of disease progression or according to clinical need.

Clarification of the patient and/or legal guardian

It is mandatory that the patient and/or his/her legal guardian are properly informed about the potential risks, benefits and adverse effects related to the treatment of breast cancer, in a clear and understandable language.

DISCUSSION OF THE CASE

In the case report presented, we were able to observe that she was a 44-year-old patient, that is, she was not at the age of standardized screening. Although she has used contraceptives for many years, she no longer has any apparent risk factors. We were able to observe that even with some arguments against its performance, self-examination can be a useful tool, as it was in the diagnosis of this patient, who noticed important changes such as unilateral depression in the right nipple, pain and papillary discharge. We also noticed that the complete anamnesis, qualified listening and detailed physical examination of the patient are extremely important and that other tests are complementary to help understand the situation, which is clearly explained when one of the physicians noticed that the evaluation of the breasts was not compatible with the radiographic report and the change in the way of performing mammography and the subsequent biopsy made a total difference in the diagnosis of this patient.

Regarding treatment, neoadjuvant chemotherapy is highly relevant in order to reduce the size of the tumor lesion and, consequently, reduce the morbidity and mortality of the mastectomy that would be performed later. Surgical removal of the breast from the adjacent lymph node chain was chosen over segmentectomy since infiltrating lobular carcinoma has a multicentric pattern and considering that the patient took about 2 years to obtain the diagnosis and, therefore, the lesion is more advanced. In this sense, radical mastectomy was an appropriate choice not only to treat but also to prevent recurrence/recurrence of the disease. It is noteworthy that follow-up with the multidisciplinary team is essential to ensure the minimization of damage and clinical, psychological, nutritional and social complications during cancer treatment in its various phases.

It is important to emphasize that the reality of the patient cited in this case is not that of the majority of Brazilian women, since most people do not undergo regular follow-up. Therefore, it is important to value campaigns such as Pink October, showing the importance of early screening in search of a better prognosis. Finally, what we can conclude in this case is that the health team should always give due importance to the patients' complaints and not let the complementary exams speak louder than the clinic.

CONCLUSION

From this study, it was possible to perceive the relevance of the discussion about breast cancer in society since it is a disease with high prevalence and important biopsychosocial impact. Often, the signs and symptoms of breast cancer do not receive due attention, which causes a delay in diagnosis and, consequently, a late intervention, which will profoundly influence the patient's prognosis. The watchful eye of the multidisciplinary team based on protocols and up-to-date scientific evidence is essential for this process to occur as early as possible, enabling a reduction in

the speed of disease progression, longer survival, and the possibility of greater comfort with palliative care in cases where the prognosis is reserved.

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