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SOCIEDADE BRASILEIRA DE MASTOLOGIA

Praça Floriano, 55, sala 801, Centro – 20031-050 – Rio de Janeiro (RJ)
Phone numebrs: (21) 2220-7711 / (21) 2220-7111
E-mail: secretaria@sbmastologia.com.br

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THE STATE OF BREAST RECONSTRUCTION IN AUSTRALIA: CHALLENGES AND OPPORTUNITIES

O estado da reconstrução mamária na Austrália: desafios e oportunidades

Emilia L. Dauway[1]*

This editorial is from the perspective of an American breast surgeon that immigrated to Australia four years ago. As the former Chief of Breast Surgery at a 750- bed hospital in Texas that treated 350 new breast cancer diagnoses a year, she was accustomed to accessing all aspects of reconstructive surgery through a large department of plastic surgery. The following are her opinions, observations and experiences in providing breast reconstruction in the US and Australia. Her point of view is both personal and professional; while providing evidential data to understand current challenges and opportunities for breast reconstruction in Australia.

Breast cancer surgery and reconstruction trends

Breast cancer is the most common cancer affecting women globally. Similarly, in Australia, approximately 18,235 new cases will be diagnosed in 2018. Of those diagnosed, less than half (48%) will have undergone a mastectomy for surgical management. It is well known that breast conserving surgery followed by adjuvant radiation therapy is as effective in survival as a mastectomy for women with early stage breast cancer. Despite having similar survival rates and early detection, many women still elect, or are advised, to have mastectomy by their physician.

Studies have demonstrated that breast reconstruction contributes to improving quality of life, as well as psychological recovery after mastectomy. Similar rates of patient satisfaction are also reported in studies comparing mastectomy with reconstruction and breast preservation. Despite these promising trends, the current rate of breast reconstruction in Australia is 8–12%[1], considerably lower than their western counterparts in the US or the UK. One in ten women in Australia will undergo breast reconstruction, in comparison to 3 in 10 in the UK and 5 in 10 in the United States. Is it unreasonable to compare breast reconstruction trends between Australia, the United States and the UK?

HEALTHCARE SERVICE DELIVERY CHALLENGES

Land mass and population

To gain a better perspective, the geographical size of the United States is approximately 9.8 million km^2 and Australia is 7.7 million km^2. Although the size in land mass is nearly comparable, US population is approximately 320 million; while Australia's population is less than a tenth of the U.S., at 27 million, (smaller than the state of Texas). While Australia and the U.S. deliver healthcare to large populations spread over millions of kilometers and miles, the UK faces the challenge of population density in providing care to 65 million people spread over 242,000 km^2. In being the most arid inhabited continent in the world, Australia's population is distributed more widely along coastal areas affording access to water. What may be surprising to many is the lack of water in the middle of the country, and the potential for severe droughts every 18 years limits residential opportunities. As these data points suggest, each country faces unique challenges in addressing accessibility.

As one can imagine, Australia's geographical landscape is unique and presents a significant challenge in providing access to healthcare services for those who live or work in remote regions.

[1]Mater Hospital – Gladstone, Queensland, Australia.
***Corresponding author:** dredauway@mercycq.com
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Barriers to breast reconstruction

Immigrating to Australia, where more skilled healthcare professionals are needed to provide care in remote areas, didn't seem too intimidating, after spending 7 years working on the island of Kauai, Hawaii, with limited resources (no adjuvant radiation nor stereotactic biopsy capabilities). What became apparent was that one develops a more grounded perspective of the issues, challenges, or barriers that impact access, and more importantly, the choices patients make about their treatment options.

A recent review by Roder et al.[2], showed that mastectomy rates vary across demographic and geographic areas. Mastectomy was found more prevalent in regional remote locations and lower socio-economic areas. It is unclear whether lack of resources, such as access to radiation treatment, was a contributing factor. It also indicated that surgeons with low breast cancer surgical caseloads were more likely to perform mastectomy[2]. Not all surgeons who perform mastectomy have training and expertise to perform oncoplastic surgical techniques, especially in remote areas. The Breast Surgeons of Australia and New Zealand (Breast Surg ANZ) is an organization committed to breast subspecialty training with exposure to a broad range of reconstruction techniques. Members are required to participate in compulsory audits to maintain quality assurance and offer the best available breast cancer care[1]. Unfortunately, many newly trained oncoplastic breast surgeons choose to reside in metropolitan areas despite a lack of surgical employment opportunities for them. This is one area that can be improved. For example, incentivizing young breast surgeons to work in remote areas of need would provide needed services and maintain their skills, while gaining mentorship during the early phases of their surgical career.

Adequate access to information

The Breast Cancer Network Australia (BCNA) conducted a breast reconstruction survey in 2012 to identify barriers for women seeking access to breast reconstruction. One of the findings was that some women surveyed found it difficult to access general information about breast reconstruction[3]. In the US, Alderman et al.[4] reported that when women are provided adequate information concerning their breast reconstruction options, they were more likely to consider mastectomy and immediate reconstruction when appropriate. BCNA reported 10% of women surveyed did not have discussions about breast reconstruction, nor were they offered breast reconstruction as a post-mastectomy option. Others reported feeling overwhelmed by their cancer diagnosis and unable to adequately consider reconstruction options if offered[3].

What we may underestimate is the role a surgeons' attitude towards breast reconstruction can play in significantly influencing a woman's choice[4]. Education for breast cancer treatment options that allows patients to make an informed decision is important. Many patients are justifiably fearful. However, with medical professionals providing appropriate information as well as reasonable time for the patient to reflect on their options, we can (and should) reduce fear-based decision making. It is well understood that a successful breast reconstruction starts with a good mastectomy. Regardless of a surgeon's ability to perform a reconstruction, discussions and collaboration with an oncoplastic surgeon prior to mastectomy provides the best possible oncologic and aesthetic outcome for the patient, if that is the patient's preference.

Access to affordable healthcare

Another obstacle that women can encounter is having access to affordable and timely healthcare. For example, despite differences in geography, terrain and population density, the need for access to adequate care continues to be a stalwart issue for the U.S. as well as Australia. Unlike the US, however, Australia has the benefit of both a private and public healthcare system which should (*in theory*) provide greater access to care. In the US, breast reconstruction is a mandated right (Women's Health and Cancer Right's Act-1998). And, despite a lack of universal healthcare, the costs for breast reconstruction in the US are growing as more women elect this treatment option. When considering healthcare costs in Australia, the BCNA survey identified high out of pocket costs ranging from $ 5,000-15,000 for private patients beyond the health insurance coverage. For patients choosing to have care through the public system, waiting lists times can range from 12-48 months. Immediate breast reconstruction at the time of mastectomy, when appropriate, could reduce costs and wait times.

There have been concerns that immediate breast reconstruction may delay adjuvant treatments which would then impact survival. Evidence demonstrates the contrary: that surgical complications are not necessarily greater for women who choose breast reconstruction compared to no reconstruction[5]. Furthermore, it has been shown that the aesthetic outcomes and psychologic benefits are greater when comparing immediate reconstruction and delayed reconstruction. Not surprisingly, interest and requests for immediate breast reconstruction are increasing.

OVERCOMING HURDLES TO ACCESS

Although there are many challenges including costs and the need to train more breast surgeons with a broad range of skills, *educating women about breast cancer treatment options (including breast reconstruction) continues to be one of the greatest hurdles*. In Australia, there is an increasing awareness of the need to improve access to breast reconstruction for women who have the desire to be restored. Utilizing contemporary technology such as telehealth and Skype are just a few examples of more effective ways to distribute knowledge and education to patients. And today there are more breast reconstruction training programs. But until there are incentives that encourage remote employment, more research and an

investment in teaching opportunities, access to contemporary breast cancer care will remain elusive. In his dialogue, Republic, Plato said, "Necessity is the mother of invention." The need to expand breast reconstruction services in Australia encourages creative efforts to increase accessibility for all women regardless of geographic and demographic factors.

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ANALYSIS OF TIME INTERVAL BETWEEN BREAST CANCER DIAGNOSIS AND TREATMENT

Análise do tempo decorrido entre diagnóstico e tratamento do câncer de mama

Alessandra Formigheri[1]*, Janaina Brollo[1], Fernando Vivian[1], Rafael Maciel Grochot[1], Solange de Cassia Pezzi Copatti[1], André Borba Reiriz[1], José Mauro Madi[1], Maximiliano Cassilha Kneubil[1,2]

ABSTRACT

Introduction: Breast cancer has a good prognosis when treated early. However, the mortality rate in Brazil is still high. The time interval between radiological suspicion and diagnosis/treatment impacts the survival. **Methods:** This is a retrospective cross-sectional study that assessed patients treated at a reference center, with abnormal breast imaging findings and subsequent confirmation of breast cancer, from January 2011 to June 2015. We reviewed variables related to the dates of the abnormal test result, first mastology appointment, biopsy, surgery, and the start of chemotherapy – when indicated. Time intervals were compared using the Friedman and Kruskal-Wallis tests with the software SPSS® 23.0. **Results:** We analyzed 65 patients. The median time between the abnormal test result and first mastology appointment was 35 days; between first mastology appointment and biopsy, 31 days; between biopsy and surgery, 85 days; and between surgery and chemotherapy, 137 days. The last two intervals showed significant differences ($p<0.001$). **Discussion:** Breast cancer patients had a significant delay until surgery and the start of chemotherapy. Early integration of the multidisciplinary team involved in this process and internal audits are necessary to optimize time intervals.

KEYWORDS: Breast cancer; chemotherapy; diagnosis; epidemiology; public health.

RESUMO

Introdução: O câncer de mama apresenta bom prognóstico quando tratado precocemente, entretanto, a mortalidade no Brasil continua elevada. O tempo entre suspeita radiológica e diagnóstico e tratamento tem impacto na sobrevida. **Métodos:** Foi realizado um estudo transversal e retrospectivo que avaliou pacientes atendidas em centro de referência com imagem mamária alterada e posterior confirmação de câncer de mama de janeiro de 2011 a junho e 2015. Foram revisadas variáveis relacionadas às datas do exame alterado, da primeira consulta, da biópsia, da cirurgia e do início da quimioterapia, quando indicada. Os intervalos de tempo foram comparados pelos testes Friedman e Kruskal-Wallis, pelo programa SPSS® 23.0. **Resultados:** Foram analisadas 65 pacientes. A mediana de tempo entre exame alterado e primeira consulta foi 35 dias, entre consulta na mastologia e biópsia foi 31 dias, entre biópsia e cirurgia foi 85 dias e entre cirurgia e quimioterapia foi 137 dias. Foram observadas diferenças significativas nos dois últimos intervalos ($p<0,001$). **Discussão:** As pacientes com câncer de mama apresentaram atraso significativo até a cirurgia e até o início da quimioterapia. Há necessidade da integração precoce da equipe multidisciplinar implicada nesse processo e auditorias internas a fim de otimizar os intervalos de tempo.

PALAVRAS-CHAVE: Câncer de mama; quimioterapia; diagnóstico; epidemiologia; saúde pública.

[1]Hospital Geral de Caxias do Sul – Caxias do Sul (RS), Brazil.
[2]Instituto de Biotecnologia, Universidade de Caxias do Sul – Caxias do Sul (RS), Brazil.
*__Corresponding author:__ alegheri@hotmail.com
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INTRODUCTION

Breast cancer (BC) is the most prevalent malignant neoplasm among women (excluding non-melanoma skin tumors) and the most common cause of cancer mortality in this population[1]. In Brazil, according to estimates from the National Cancer Institute (*Instituto Nacional do Câncer* –INCA), BC was responsible for 14,388 deaths in 2013, and 57,960 new cases were expected in 2016[1]. Mortality rates for this disease are still high in the country, probably due to it being diagnosed in advanced stages, especially in social classes with lower purchasing power.

Despite the high BC incidence, up to 95% of patients can be cured if diagnosed in early stages[2]. Therefore, early diagnosis is a fundamental strategy to treat this cancer. The most effective measure for early BC diagnosis is mammography since mammographic screening can reduce mortality rates by up to 40%[3]. Several clinical studies have shown that early BC diagnosis and treatment can decrease the specific mortality of this neoplasm[4-6]. Recent results demonstrate that delaying the treatment of this cancer reduces overall survival[7-11]. Nevertheless, available data on the period between finding the suspicious breast lesion and BC diagnosis and treatment are scarce, and these variables could impact the prognosis and differ according to regions of the country, depending on geographic and socioeconomic factors.

This study evaluated the time interval between radiological suspicion and BC diagnosis and treatment in a public hospital reference in oncology in Southern Brazil. Based on these results, our secondary objective was to understand the reason for the greater delay in the process and discuss strategies to optimize the flow of patients.

METHODS

This was an observational retrospective cross-sectional study, approved by the Scientific and Editorial Committee of Hospital Geral de Caxias do Sul and the Committee for Ethics of Universidade de Caxias do Sul. We assessed all consecutive patients treated at Hospital Geral de Caxias do Sul (a tertiary level III hospital, reference for the 5th Health Coordination of Rio Grande do Sul), who presented a mammographic image and/or breast ultrasound classified in categories 4 and 5 of the Breast Imaging Reporting and Data System (BI-RADS®)[12,13] between January 1, 2011 and June 30, 2015, followed by histological confirmation (via percutaneous biopsy, fine needle puncture, or excision of the lesion) of malignant breast neoplasm. After identifying the patients, the researchers reviewed the outpatient and hospital medical records. The patient characteristics analyzed related to age, ethnicity, prior history of smoking, menopausal status, modality of test with abnormal imaging, type of radiological abnormality, BI-RADS® category, histological subtype and grade, clinical stage (CS), surgical modality, and adjuvant treatment – when applicable.

We evaluated the following intervals:

- date of the abnormal imaging test until the date of the first mastology appointment;
- date of the first mastology appointment until the date of biopsy;
- date of biopsy until the date of surgery;
- date of surgery until the date of the start of chemotherapy (when applicable).

Patients were excluded if they received neoadjuvant treatment, had distant metastases at diagnosis, ductal carcinoma *in situ*, and incomplete medical records.

For the statistical analysis, we used the software SPSS® version 23.0 (SPSS® Inc.; Illinois, USA). The choice of measures of central tendency and dispersion of values that compose the samples, as well as statistical tests to compare them was based on types of distribution, according to the Shapiro-Wilk test. Values of each quantitative variable were organized and described by median, mean, and standard deviation. Qualitative data were represented by absolute and relative frequencies. We used the Friedman test to compare time intervals, and the Kruskal-Wallis test to compare three or more populations. All tests adopted a statistical significance value of 5% ($p \leq 0.05$).

Definitions

The definition used for abnormal imaging tests was based on BI-RADS®[12,13], a classification that standardized the description of reports, systematized the categorization and management of lesions, and provided an internal audit system for breast imaging quality. Lesions defined as suspicious were classified as BI-RADS 4 and 5, requiring, therefore, biopsy for anatomopathological evaluation. Category 4 is subdivided into 4A, 4B, and 4C. In group 4A, the risk of malignancy is 10%; in 4B, it is a little higher, but, usually, lower than 50%; and in 4C, this value ranges from 50 to 95%[10,12]. Category 5 should be reserved for classical tumor lesions, in which malignancy will only be ruled out after surgical evaluation of the region; in this category, the chance of malignant lesion exceeds 95%[12,13].

We used the 8th edition of the BC staging system recommended by the Union for International Cancer Control (UICC), known as the TNM Classification of Malignant Tumors. This system is based on the anatomic extent of the disease, taking into account the characteristics of the primary tumor (T), the nature of lymph nodes from the chains of lymphatic drainage of the organ in which the tumor is located (N) and the presence or absence of distant metastases (M)[14].

RESULTS

We evaluated 88 patients with abnormal imaging test (BI-RADS 4 and 5) and confirmation of breast neoplasm after biopsy from January 1, 2011 to June 30, 2015. Out of the total sample, we excluded three women who did not have a BI-RADS category

described in the imaging test, two who had carcinoma *in situ*, ten who underwent neoadjuvant chemotherapy, five who had metastases at diagnosis, two with no relevant information on their medical records, and one for not being within the predetermined period. Thus, this analysis included 65 patients.

The mean age was 58.9 years. Table 1 summarizes the pathological and clinical characteristics of the patients. Among them, 75.4% were of Hispanic origin, 81.5% were non-smokers, and 76.9% were in post-menopause. Thirty-three patients (50.8%) were referred to the mastology center due to a suspicious lesion found in mammographic screening, and 32 (49.2%) presented abnormal breast ultrasound. The most frequent lesion in imaging tests was the presence of an isolated nodule — 84.6% of cases. Patients with lesions classified as BI-RADS 4 at diagnosis represented 86% of the sample, and BI-RADS 5, 14%. Regarding the histological subtype, 73.8% had invasive carcinoma of no special type (ductal), and 16.9% presented invasive lobular carcinoma; 63.1% had histological grade 2 and 29.2%, grade 3. Forty-one patients had CS IA (50.8%) and IB (12.3%) at diagnosis, while 15.4% presented CS IIA; 3.8%, CS IIB; and 7.7%, CS IIIA.

With respect to treatment, conservative breast surgery (lumpectomy) represented 66.2% of cases, and 73.8% of patients initially underwent sentinel lymph node biopsy. Concerning adjuvant treatment, 75.4% of subjects underwent radiotherapy; 53.8%, chemotherapy; and 87.7%, hormone therapy (Table 2).

Table 3 presents the time intervals between the abnormal test result and diagnosis and treatment. The median time between the date of the abnormal test result and the first mastology appointment was 35 days; between the first mastology appointment and biopsy was 31 days; between biopsy and surgery was 85 days; between surgery and the start of chemotherapy — when indicated —, was 137 days. The last two intervals showed significant differences ($p<0.001$). The interval between surgery and the start of chemotherapy was higher than all the other ones analyzed. Also, the period between biopsy and surgery was superior to that of abnormal test result until the first mastology appointment, and of the first mastology appointment until biopsy, with no significant difference between the last two.

The medians of the intervals presented no significant differences when we analyzed the patients according to their clinical stage (Table 4).

DISCUSSION

Several factors influence the overall survival of BC patients. Mammographic screening plays a fundamental role, reducing the mortality from this type of cancer by 30–40%, as it considerably increases the chance of early diagnosis[3,5,6]. On the other hand, the delay in starting adjuvant chemotherapy is associated with a worse prognosis for patients with breast neoplasm[7-11]. In addition, other usually underestimated and not routinely assessed factors might be related to a worse prognosis, such as the time interval from clinical and radiological suspicion to breast cancer diagnosis and treatment[15-19].

Table 1. Population characteristics.

Variables (n=65)	N	%
Age	58.9±10.4	
Ethnicity		
White	49	75.4
Black	2	3.1
Other	14	21.5
Tobacco use		
No	53	81.5
<20 packs/year	9	13.8
>20 packs/year	3	4.6
Menopausal status		
Pre-menopause	15	23.1
Post-menopause	50	76.9
Abnormal test result		
Ultrasound	32	49.2
Mammography	33	50.8
Type of abnormality		
Nodule	55	84.6
Microcalcifications	3	4.6
Nodule + microcalcifications	4	6.2
Breast asymmetry	3	4.6
BI-RADS		
BI-RADS 4	36	55.4
BI-RADS 4A	1	1.5
BI-RADS 4B	4	6.2
BI-RADS 4C	10	15.4
BI-RADS 5	14	21.5
Histological type		
Lobular	11	16.9
Invasive carcinoma of no special type	48	73.8
Other	6	9.2
Histological grade		
1	5	7.7
2	41	63.1
3	19	29.2
Clinical stage		
IA	33	50.8
IB	8	12.3
IIA	10	15.4
IIIB	9	13.8
IIIA	5	7.7

When we evaluated the time interval between the date of the abnormal imaging test and the first mastology appointment, at our institution, we found a median of 35 days. Although there is no ideal period for this interval, we consider this result acceptable, as it demonstrates an efficient flow of patients with suspicious lesions from Basic Health Units (*Unidades Básicas de Saúde* – UBSs) to the mastology center. Also, this information suggests that family doctors and gynecologists from UBSs in Caxias do Sul are prepared for the detection and appropriate referral of lesions suspicious for BC.

When we analyzed the time intervals between the first mastology appointment and biopsy, and between biopsy and surgery, we found medians of 31 and 85 days, respectively. According to Law no. 12,732, of November 22, 2012, the cancer patient will receive, free of charge, all treatments necessary from the public health system (*Sistema Único de Saúde* – SUS) within up to 60 days counted from the date the report of diagnosis is signed for the patient to start the first treatment — in compliance with the therapeutic need the case requires. Olivotto et al.[18] demonstrated that a delay in diagnosis is associated with a greater axillary lymph node involvement and larger tumors. However, in our study, the medians of the intervals presented no significant differences when we analyzed the patients according to their clinical stage.

Among the patients submitted to adjuvant chemotherapy, the median between the date of surgery and the start of chemotherapy was 137 days. The literature has no data establishing an ideal value for this time interval. In an American study that analyzed patients using records of the National Comprehensive Cancer Network (NCCN), Vandergrift et al.[11] found a median of six weeks between surgery and the start of chemotherapy. The American Society of Clinical Oncology (ASCO) suggests that the interval between diagnosis and treatment should not exceed 120 days[20,21]. Gagliato et al.[7] revealed that an interval between surgery and start of chemotherapy exceeding 60 days is associated with worse survival, particularly for patients in stage III, and with triple-negative and HER2 positive breast tumors. In a

Table 2. Treatments undergone.

Variables (n=65)	N	%
Surgery		
Lumpectomy/Quadrantectomy	43	66.2
Nipple-sparing mastectomy	2	3.1
Skin-sparing mastectomy	1	1.5
Modified radical mastectomy	19	29.2
Sentinel lymph node biopsy	48	73.8
Axillary drainage	25	38.5
Adjuvant radiotherapy	49	75.4
Adjuvant chemotherapy	35	53.8
Adjuvant hormone therapy	57	87.7
Tamoxifen	32	56.1
Anastrozole	12	21.1
Tamoxifen>Aromatase inhibitor	8	14.0
Aromatase inhibitor>Tamoxifen	5	8.8
Ovarian suppression	7	10.8

Table 3. Time intervals.

Interval (in days)	Mean±SD (median)	Minimum	Maximum
Abnormal test result – mastology appointment	49.1±44.40 (35.0)[a]	7	248
Mastology appointment – biopsy	44.3±46.0 (31.0)[a]	0	240
Biopsy – surgery	85.1±40.0 (85.0)[b]	0	174
Surgery – start of chemotherapy	153.5±99.5 (137.0)[c]	24	397

SD: standard deviation; medians followed by identical letters do not differ among themselves.

Table 4. Time interval according to clinical stage.

Interval	Clinical stage					p-value*
	Mean±SD (median)					
	1A (n=33)	1B (n=8)	2A (n=10)	2B (n=9)	3A (n=5)	
Abnormal test result – mastology appointment	47.4±46.4 (34.0)	69.8±77.3 (48.0)	43.2±18.2 (41.0)	45.8±22.3 (41.0)	45.0±32.3 (26.0)	0.747
Mastology appointment – biopsy	57.2±57.5 (37.0)	36.0±28.8 (30.0)	31.8±20.7 (28.0)	30.9±30.1 (31.0)	21.8±12.4 (27.0)	0.403
Biopsy – surgery	81.8±41.6 (83.0)	74.8±47.1 (86.0)	91.6±36.2 (90.5)	98.2±38.0 (110.0)	87.0±35.4 (98.0)	0.734
Surgery – chemotherapy	146.1±82.0 (125.0)	107.8±61.3 (108.0)	186.0±130.7 (173.0)	209.7±107.7 (268.0)	109.4±140.6 (47.0)	0.141

SD: standard deviation; *Kruskal-Wallis test.

similar study, Yu et al.[20] demonstrated that patients with more aggressive molecular subtypes, such as triple-negative, luminal B, and HER2 positive tumors, had worse survival when this delay was longer than eight weeks. Trufelli et al.[22] showed that, for each month of delay in beginning the adjuvant treatment, the risk of death increases 1.3%, representing a risk factor independent from other known ones.

Considering that BC is a heterogeneous and complex disease, we believe that one way of reducing these time intervals is integrating the multidisciplinary team primarily in the process of diagnosis and treatment. The patient with this cancer must be early monitored by a specialized multidisciplinary team that includes physicians (mastologist, clinical oncologist, radiologist, radiation oncologist, pathologist), nurse, psychologist, social worker, and physiotherapist, in order to improve the intervals between diagnosis and treatment and facilitate the entire process. Studies indicate that a multidisciplinary team caring for the patient optimizes the work and reduces the mortality rate, in addition to improving outpatient and hospital management[23].

Furthermore, we believe that routine internal audits of time intervals between radiological suspicion and diagnosis and treatment are fundamental to the excellence in BC treatment in reference centers. As important as the availability of modern chemotherapy and radiotherapy regimens and state-of-the-art equipment is decreasing time intervals between diagnosis and treatment, as they are also an indicator of the quality of health services and directly affect the survival of patients.

The strengths of our study include the comprehensive nature of the database with clinical and pathological characteristics of the patients, surgery description, adjuvant treatments received, and a rigorous assessment of intervals between the abnormal test result and diagnosis and treatment. In addition, the population of our study was quite homogeneous, consisting of patients referred from UBSs, treated exclusively by the SUS, who had their biopsies in our service and received only adjuvant treatments, since we excluded from this study those who received neoadjuvant chemotherapy or hormone therapy. On the other hand, we understand the limitations of our study, which involve its retrospective nature, the reduced sample of patients assessed, and the lack of evaluation of possible psychosocial factors that could contribute to the delay in diagnosis, such as fear of a cancer diagnosis, denial of the disease, and understanding of the process.

BC patients treated in our service had a significant delay between biopsy and surgery, as well as between surgery and the start of chemotherapy. Early integration of the multidisciplinary team involved in this process and routine internal audits are necessary to optimize the time intervals between diagnosis and treatment, and eliminate the negative impact on patient survival.

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VALUE OF THE INTRAOPERATIVE CYTOLOGY EXAMINATION OF SENTINEL LYMPH NODE IN BREAST CANCER

Valor do exame citológico intraoperatório do linfonodo sentinela no câncer de mama

Talita Siemann Santos Pereira[1], Guilherme Loureiro Werneck[2], Henrique de Castro Rodrigues[3], Ana Helena Pereira Correia[4], Flávia Clímaco[4], Afrânio Coelho de Oliveira[4]*

ABSTRACT

Objective: Evaluate the value of imprint cytology in the intraoperative analysis of sentinel lymph node (SLN) in patients with breast cancer. **Methods**: An agreement study for the evaluation of the imprint cytology technique as a diagnostic test for intraoperative SLN among patients diagnosed with breast cancer from January 2007 to January 2017. **Results**: We studied 210 cases of breast cancer patients submitted to intraoperative sentinel node imprint cytology, aged between 24 and 86 years (mean age 59 years and median age 60 years). The sensitivity of the intraoperative study was 58.3% (95%CI 46.1–69.8%) and the specificity was 97.8% (95%CI 93.8–99.5). The positive predictive value (PPV) was 93.3% (95%CI 81.7–98.6) and the negative predictive value (NPV) was 81.8% (95%CI 75.1–87.4). From the analyzed variables, the presence of macrometastasis was the only one that significantly increased the sensitivity of the imprint to 73.2% (95%CI 59.7–84.2), while micrometastasis presented a sensitivity of only 6.3% (95%CI 0.2–30.2). **Conclusion**: The use of imprint cytology in the intraoperative SLN study showed good accuracy in predicting axillary status. However, the surgeon and pathologist are fully aware of the set of clinical and histological variables that can influence the sensitivity of the method.

KEYWORDS: Sentinel lymph node; breast cancer; cell biology.

RESUMO

Objetivo: Avaliar o valor do *imprint* citológico na análise intraoperatória do linfonodo sentinela (LS) em pacientes com câncer de mama. **Métodos**: Estudo de concordância para avaliação da técnica do *imprint* citológico como teste diagnóstico do LS no intraoperatório, entre pacientes com diagnóstico de câncer de mama, no período de janeiro de 2007 a janeiro de 2017. **Resultados**: Foram estudados 210 casos de pacientes com câncer de mama submetidas à citologia de impressão (IC) do linfonodo sentinela no intraoperatório, com idade entre 24 e 86 anos (média de 59 anos e mediana de 60 anos). A sensibilidade do estudo intraoperatório foi de 58,3% (IC95% 46,1–69,8) e a especificidade de 97,8% (IC95% 93,8–99,5). O valor preditivo positivo (VPP) foi de 93,3% (IC95% 81,7–98,6) e o valor preditivo negativo (VPN) de 81,8% (IC95% 75,1–87,4%). Das variáveis analisadas, a presença de macrometástase foi a única que aumentou significativamente a sensibilidade do *imprint* para 73,2% (IC95%, 59,7–84,2%), enquanto na micrometástase apresentou sensibilidade de apenas 6,3% (IC95% 0,2–30,2). **Conclusão**: A utilização do *imprint* citológico no estudo intraoperatório do LS apresentou boa acurácia na previsão do *status* axilar. Entretanto, é importante o pleno conhecimento, pelo cirurgião e patologista, do conjunto de variáveis clínicas e histológicas que podem influenciar a sensibilidade do método.

PALAVRAS-CHAVE: Linfonodo sentinela; câncer de mama; citologia.

Study carried out at the Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro – Rio de Janeiro (RJ), Brazil.
[1]Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro – Rio de Janeiro (RJ), Brazil.
[2]Instituto de Estudos em Saúde Coletiva, Universidade Federal do Rio de Janeiro – Rio de Janeiro (RJ), Brazil.
[3]Serviço de Epidemiologia e Avaliação, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro – Rio de Janeiro (RJ), Brazil.
[4]Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro – Rio de Janeiro (RJ), Brazil.
***Autor correspondente:** afranio.co@gmail.com
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INTRODUCTION

Breast cancer is the second most frequent cancer in the world and the one with the highest incidence among women in Brazil. According to the National Cancer Institute (INCA), the number of new cases of breast cancer expected for Brazil in 2016 was 57,960, with an estimated risk of 57 cases per 100,000 women[1].

The early diagnosis of breast cancer has increased mainly because of mammography screening programs. Thus, less aggressive and more conservative treatments have been developed, with good cosmetic results and without affecting the control of the disease. In the twentieth century, the treatment of breast cancer evolved from the Halsted radical mastectomy to conservative surgery[2].

The work that consolidated the conservative surgery was a result of the classic study by Veronesi et al., who did not demonstrate difference in disease-free survival or overall survival between the groups (mastectomy vs. conservative surgery and radiotherapy). Based on these results, they concluded that the mastectomy subjected the patients to unnecessary mutilations[3].

Despite the progression to conservative breast surgery, the only method that made it possible to evaluate the presence of axillary lymph node metastasis was the complete axillary lymphadenectomy of levels I, II and III according to the Berg classification, exposing large numbers of patients to sequelae, and without greater therapeutic benefits, especially when indicated in early-stage tumors[4,5].

In 1977, Cabanas proposed the concept of sentinel lymph node (SLN) in solid epithelial tumors, which consisted of the hypothesis that lymph nodes receiving the first lymphatic drainage of the tumor could be removed by smaller surgery and examined by means of an intraoperative study with the intention of determining the need for regional lymphadenectomy[6].

The first study on SLN research in breast cancer patients was performed by Giuliano et al. at the John Wayne Cancer Institute at Saint John's Hospital and Health Cancer in Santa Monica, California, in 1994. It was proven that the technique improved staging accuracy and had the potential to replace axillary lymphadenectomy[7]. Since then, a large number of studies and publications have found that SLN determines lymph node status in early breast cancer with high accuracy, demonstrating that it is safe to omit axillary lymphadenectomy in cases of SLN without metastatic disease[8-10].

In 2010, a study published by Giuliano et al. concluded that, despite the potential for residual axillary disease after LS biopsy, failure to perform axillary lymphadenectomy with metastatic involvement of one to two lymph nodes may provide excellent regional control and may be considered a treatment option for early-stage breast cancer patients treated with conservative surgery, tangential radiotherapy and adjuvant systemic therapies[11].

The techniques employed/utilized for the intraoperative study of SLN may be imprint cytology and frozen section. Imprint cytology can provide rapid, technically feasible diagnosis by preserving tissue for the permanent section. By freezing the material, there is the disadvantage that the sections can undergo artefactual alterations, the tissues are consumed and the procedure may take a longer time to execute[12]. However, the most important question is whether the intraoperative assessment of SLN, regardless of the technique used, is performed with a high degree of precision.

Considering the importance and the impact in breast cancer treatment and the minimally invasive approach that SLN represents, it is relevant that a referral service in the treatment of breast cancer obtains its data and evaluate the results of its intraoperative study. Therefore, the present study was performed with the purpose of demonstrating the value of imprint cytology in the evaluation of SLN in patients with breast cancer.

MATERIALS AND METHODS

This is an agreement study to the evaluation of the imprint cytology technique as an intraoperative LS diagnostic test in patients diagnosed with breast cancer at the University Hospital Clementino Fraga Filho (HUCCF) of Universidade Federal do Rio de Janeiro (UFRJ), in the period from January 2007 to January 2017. The definitive histopathological examination was used as the gold standard.

The intraoperative study was performed using the imprint cytology technique. The SLN examined was cut in two parts along its largest axis, and the imprint cytology of each of the obtained halves was performed. The cytology slides of the imprint were stained with toluidine blue or hematoxylin-eosin (H-E) and examined under an optical microscope to investigate cytological features of malignancy.

The sentinel lymph node was sectioned in slices with approximately 2 mm in thickness, fixed in 10% formalin solution, and sent in its entirety for routine histopathological processing, with inclusion in paraffin and obtaining definitive histological sections, stained with H-E. In cases where the first histopathological cut was negative, two additional cut levels of 200 µm each were stained with H-E. In the cases of infiltrating lobular carcinoma, the routine also included an anti-cytokeratin immunohistochemical test.

The data sources used were the database of the pathological anatomy service and notes on physical medical records. The variables evaluated in the database were the result of intraoperative imprint cytology and the definitive SLN report. In the medical records, the following data were collected: age (<50 years, 50 to 59 years, 60 to 69 years, ≥70 years), menopause, surgery performed, year of procedure, tumor size, histological type, histological grade, estrogen receptor, progesterone receptor, Her-2 gene, Ki67 antigen, number of evaluated SLN, axillary lymphadenectomy performed after SLN biopsy, axillary lymphadenectomy

after definitive assessment, final histopathology of axillary lymphadenectomy, type of SLN metastasis (micrometastasis or macrometastasis), presence of vascular embolization, neoadjuvant chemotherapy and staging (TNM).

The results of the intraoperative SLN assessment by means of imprint cytology were compared with the results of the definitive diagnosis. The sensitivity and specificity of the intraoperative examination were analyzed, as well as the positive and negative predictive values throughout the series of patients. Later, we studied the same parameters according to available clinical and histological data: age and menopause status, histological type and size of the tumor, presence of vascular embolism, histological grade, hormonal receptor status, neoadjuvant chemotherapy and size of nodal metastases.

Statistical analysis was performed using the Excel® and Stata® software. The overall results for each patient were classified as true positive (TP — presence of metastatic cells in the intraoperative examination and final histological examination), false positives (FP — presence of metastatic cells in the intraoperative examination, but not in the final histological examination), true negatives (TN — absence of metastatic cells in the intraoperative and final examinations) or false negatives (FN — presence of metastatic cells in the final histological examination that were not initially observed in the intraoperative examination).

Intraoperative studies were performed by different pathologists from the pathology department of HUCCF/UFRJ.

RESULTS

A total of 213 cases were selected. Three patients with incomplete results were excluded from the pathological anatomy service database. A total of 210 patients, all female, aged between 24 and 86 years, with an average of 59 years and a median of 60 years, were analyzed. Among the 210 patients, 172 (81.90%) were postmenopausal.

A total of 112 patients (53.33%) underwent conservative surgery and 98 (46.67%) underwent mastectomy. The mean tumor size in the final histopathological evaluation (pT) was 2.86 cm. Regarding staging, 64 (30.47%) were found in stage I, 120 (57.14%) in stage II, and 26 (12.39%) in stage III. Fifteen patients (7.14%) underwent neoadjuvant chemotherapy. The number of sentinel lymph nodes evaluated intraoperatively by imprint cytology was 510, with a mean of 2.4 lymph nodes/patient.

In the histological subtypes, 154 (73.33%) invasive ductal carcinomas were found (59 grade 3, 71 grade 2, 24 grade 1), 21 (10%) lobular carcinomas, eight (3.8%) ductal carcinomas *in situ* and 27 12.85%) special subtypes, including, metaplastic (five), mucinous (four), tubular (three), papilar (five), micropapillary (four), spinal (five) and cribriform (one). The neoplastic embolization detected in the surgical specimen containing the carcinoma was present in 40 (19.04%) cases.

The immunohistochemical examination detected positivity for the estrogen receptor in 170 (80.95%) and for the progesterone receptor in 167 (79.52%) patients. Ki67 and Her2 were evaluated in 97 (46.20%) cases, and Her2 expression in 14 (6.6%) patients. Among the cases, we found 52 (24.76%) luminal A, 28 (5.9%) luminal B, 16 (7.61%) triple negatives and two (0.95%) pure Her2.

The correlation of the clinical-pathological variables of the sample with the intraoperative cytological imprint of the SLN are described in Table 1.

Table 1. Correlation between clinical and pathological variables and imprint cytology.

Variables	Number of cases	Positive SLN *on imprint*	Sensitivity (CI)
Age (years)			
<50	49	12	50% (95%CI 29,1–70,9)
50–59	60	16	77.8% (95%CI 52.4–93.6)
60–69	62	12	63.2% (95%CI 38.4–83.7)
>70	39	5	36.4% (95%CI 10.9–69.2)
Menopause			
Yes	172	37	60.7% (95%CI 46.8–73.5)
No	38	8	50% (95%CI 24.7–75.3)
Size (pT)			
T1	77	12	62.5% (95%CI 35.4–84.8)
T2	114	26	54.3% (95%CI 39–69.1)
T3	19	7	70% (95%CI 34.8–93.3)
Histological type			
IDC	154	37	61.8% (95%CI 47.7–74.6)
Grade 1	24	2	25% (95%CI 3.19–65.1)
Grade 2	71	21	72% (95%CI 50.6–87.9)
Grade 3	56	12	60% (95%CI 36.1–80.9)
ILC	21	4	36.4% (95%CI 10.9–69.2)
Others	27	4	66.7% (95%CI 22.3–95.7)
Estrogen receptor			
Positive	170	40	58.7% (95%CI 45.6–71)
Negative	40	5	55.6% (95%CI 21.2–86.3)
Neoplastic embolization			
Yes	40	18	72,7% (95%CI 49.8–89.3)
No	170	27	52% (95%CI 37.4–66.3)
Neoadjuvant Chemo			
Yes	15	-	-
No	195	45	60,9% (95%CI 48.4–72.4)
Metastasis size			
Micro	16	1	6,3% (95%CI 0.2–30.2)
Macro	56	41	73,2% (95%CI 59.7–84.2)

CI: confidence interval; IDC: infiltrating ductal carcinoma; Chemo: chemotherapy; ILC: infiltrating lobular carcinoma.

In the intraoperative imprint cytology, the result was positive in 45 patients (42%), with macrometastasis present in 44(97.78%) and micrometastasis in one (2.22%). Among these positive cases, 42 (93.33%) were true positives. Among the 165 (78.57%) negative intraoperative sentinel lymph nodes, 135 (81.81%) were true negatives. In the final histopathological study, 72 patients (34.28%) presented metastasis in the sentinel lymph node, with 56 (77.78%) macrometastases and 16 (22.22%) micrometastases. The sensitivity of the intraoperative study was 58.3% (95%CI 46.1–69.8) and the specificity was 97.8% (95%CI 93.8–99.5). The PPV was 93.3% (95%CI 81.7–98.6) and the NPV was 81.8% (95%CI 75.1–87.4) (Table 2).

Two of the three patients who presented false positive results were aged between 50 and 59 years, and one was aged over 70 years old. All of them had grade 2 infiltrating ductal carcinoma, positive hormone receptors and two presented neoplastic embolization in the histopathological result. One patient underwent axillary lymphadenectomy. None of the patients performed neoadjuvant chemotherapy. One case presented a tumor size equal to 5 cm, one equal to 2 cm, and another equal to 1 cm.

Among the 30 patients (14.29%) with false negative results, 12 (40%) were younger than 50 years, four (13.34%) were aged between 50 and 59 years, seven (23.33%) were aged between 60 and 69 years, and seven (23.33%) were older than 70 years. Twenty-six (86.6%) were positive hormones and 21 (70%) had infiltrating ductal carcinoma, of which eight were grade 3, seven (23.33%) were infiltrating lobular carcinoma, one (3.33%) papillary and one (3.33%) tubular. In the positive sentinel lymph nodes (30/210), there were 15 cases of macrometastasis and 15 cases of micrometastasis. Regarding tumor size, six (20%) had a mean of 1.28 cm, 21 (70%) of 3.32 cm and three (10%) with a mean of 7.5 cm. In two patients, axillary lymphadenectomy was performed at the same surgical time, and one case presented metastasis in the other lymph nodes, and 12 (40%) underwent axillary lymphadenectomy in a second procedure, of which five presented metastasis in the sentinel lymph node only. Among the 16 patients who were not submitted to axillary lymphadenectomy, 12 (75%) presented micrometastasis in the SLN.

Among the 45 patients who presented with positive intraoperative SLN, 40 underwent axillary lymph node dissection at the same surgical time, and two after the final histopathological study, totaling 42 (20%) patients with axillary lymph node dissection after the SLN biopsy. Only 19 (45.24%) presented positive sentinel nodes, with a mean of 10.73 resected lymph nodes.

Regarding the variables studied in this cohort, the intraoperative study showed sensitivity of 50% (95%CI 29.1–70.9) and specificity of 100% (95%CI 86.3–100) in the patients aged under 50 years (23.33%). In the 50-59 age group (28.57%), sensitivity was 77.8% (95%CI 52.4–93.6) and specificity was 95.2% (95%CI 83.8–99.4). Among those aged 60-69 years (29.52%), sensitivity was 63.2% (95%CI, 38.4–83.7) and specificity was 100% (95%CI 91.8–100). Among the patients aged over 70 years (18.57%), sensitivity was 36.4% (95%CI 10.9–69.2) and specificity was 96.4% (95%CI 81.7–99,9) (Figure 1).

Patients who underwent neoadjuvant chemotherapy (15/210) did not present positive lymph nodes in the intraoperative study. The true negatives corresponded to 80% of the cases and the false negatives to 20%. In the patients who did not undergo neoadjuvant chemotherapy, the true negatives were 63.07% and the false negatives 13.84%; the imprint sensitivity in these cases was 60.9% (95%CI 48.4–72.4).

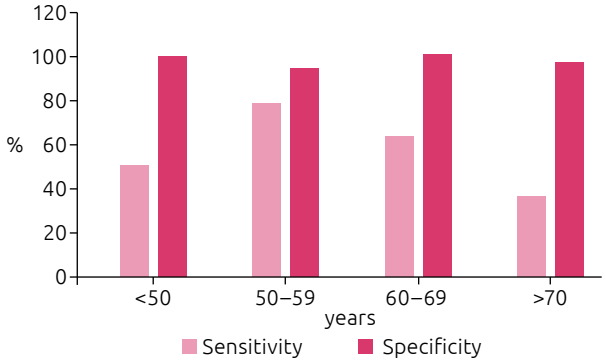
Regarding the histological type, in the patients with infiltrating ductal carcinoma, the intraoperative study presented a sensitivity of 61.8% (95%CI 47.7–74.6) and specificity of 97% (95%CI 91.4–99.4) with an NPV of 82.1% (95%CI 73.9–88.5). Among the patients with infiltrating lobular carcinoma, the sensitivity was 36.4% (95%CI 10.9–69.2) and 100% specificity (95%CI 69.2–100), with a negative predictive value of 58, 8% (95%CI 32.9–81.6). Other special subtypes resulted in sensitivity of 66.7% (95%CI 22.3–95.7) and specificity of 100% (95%CI 83.9–100) (Figure 2).

The T1 tumor size resulted in a sensitivity of 62.5% (95%CI 35.4–84.8), specificity of 96.7% (95%CI 88.7–99.6) and PPV of 83.3% (95%CI 51.6–97.9). Among patients with T2 tumors, the intraoperative study showed a sensitivity of 54.3% (95%CI 39–69.1) and specificity of 98.5% (95%CI 92.1–100) with PPV of 96.2% (95%CI 80.4–99.9). In those with T3 tumors, sensitivity was 70% (95%CI 34.8–93.3), 100% specificity (95%CI 66.4–100) and 100% PPV (95%CI 59–100).

In the cases with positive estrogen receptor, the sensitivity was 58.7% (95%CI 45.6–71) and the specificity was 97.2% (95%CI 92–99.4).

Table 2. Correlation between imprint cytology and definitive histopathological study.

Imprint cytology n (%)		Definitive histopathological study	
		Positive, n (%)	Negative, n (%)
Positive	45 (21.42)	42 (20)	3 (1.42)
Negative	165 (78.58)	30 (14.29)	135 (64.29)
Total	210 (100)	72 (34.29)	138 (65.71)



IDC: Infiltrating ductal carcinoma; ILC: infiltrating lobular carcinoma.

Figure 1. Correlation between imprint cytology and age.

The positive predictive value was 92.5% (95%CI 79.6–98.4), and the negative predictive value was 80% (95%CI 72.1–86.5).

The presence of macrometastasis resulted in sensitivity in the intraoperative study of 73.2% (95%CI 59.7–84.2), and for micrometastasis, the sensitivity was 6.3% (95%CI 0.2–30.2), with significant difference. Among the 16 cases with micrometastasis, only one was intraoperatively positive, with 93.75% being false negative. In the 56 cases of macrometastasis, 41 were intraoperatively positive, with 26.78% being false negative (Figure 3).

The presence of neoplastic embolization in the final histopathological study resulted in sensitivity of 72.7% (95%CI 49.8–89.3) and specificity of 88.9% (95%CI 65.3–98.6), with a positive predictive value of 88.9% (95%CI 65.3–98.6). In cases without neoplastic embolization, sensitivity was 52% (95%CI 37.4–66.3) and specificity was 99.2% (95%CI 95.4–100).

DISCUSSION

Breast cancer is a common pathology among women and its incidence tends to increase with age. The aging of the population and the improved quality of life in the elderly population make it an important public health problem[13]. In the present study, 48.09% of the patients were aged 60 years or older, and the mean age was 59 years. These percentages are slightly lower than in other studies, which indicate that over 50% of breast cancer patients are aged 65 years or older, and about 30% are over 70 years of age[14,15].

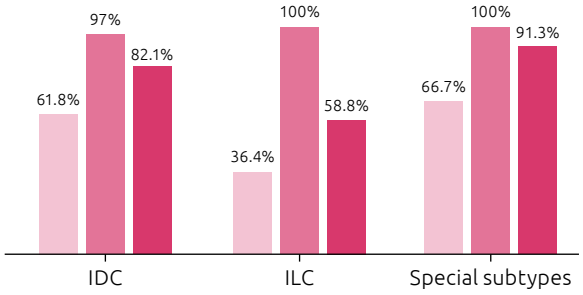


Figure 2. Correlation between imprint cytology and histological types.

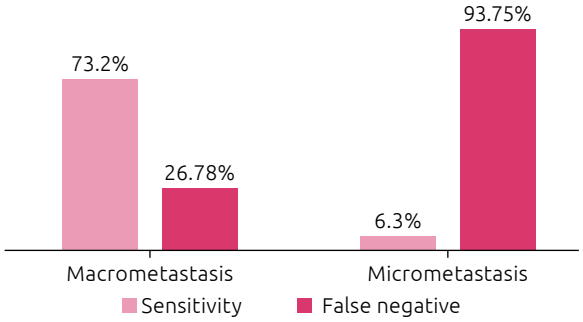


Figure 3. Correlation of sensitivity and false negative rate with lymph node metastasis size.

Strategies for the early detection of cancer are aimed at the diagnosis of cases in the early stages of their natural history. In middle- and low-income countries, breast cancers are predominantly diagnosed at more advanced stages[16]. In the present study, the tumors presented a mean of 2.86 cm in diameter and 57.14% of the patients had stage II breast cancer. As the accuracy of SLN in determining lymph node status in cancer is greater in the initial stage, smaller tumors are expected to be found in the SLN analysis studies, as can be observed in those carried out in first world countries, with an average of 12 to 15 mm, different from the results in this study[17,18].

The imprint sensitivity in the intraoperative study in our study was 58.3%, and the specificity was 97.8%. A study conducted by Pugliese et al., with 385 cases, presented results similar to the present study, with a sensitivity of 55% and specificity of 100%[19]. However, a study published in 2004 with 250 patients presented a low imprint sensitivity (34%), which is a consequence of the high proportion of micrometastases among their positive cases (42/102)[20]. This variation in sensitivity can be evidenced in the meta-analysis published by Tew et al. in 2005, which analysed 31 studies and showed a mean sensitivity of 63%, ranging from 34 to 95%, and a mean specificity of 99%, varying from 94 to 99%[21]. The heterogeneity of these studies is explained by the inclusion criteria (tumor size, histological subtype, presence of palpable axillary lymph nodes), variations in the cytology technique and differences in the histological technique used by the laboratory to examine the removed lymph node (section thickness, inclusion of the entire lymph node region, and use of immunohistochemical techniques).

The cases of false positives were found in three sentinel lymph nodes from the studied sample. These cases were also reported by Lee et al. in 2002 and Ravichandran et al. in 2004, who found one between 155 and three out of 132 cases, respectively[22,23]. False positives can be explained by the presence of isolated tumor cells ITC = or a focus of micrometastasis that are completely removed on the imprinted surface or by the presence of epithelial histiocytes, lymphocytes and tumefied endothelial cells that can be confused with tumor cells[21].

When studying the variables, an increase in sensitivity could be observed in younger patients, aged under 60 years, which can be explained by the fact that these women tend to present bigger, more aggressive tumors, and higher histological grade. Consequently, lymph node metastases are greater and the cellular atypia is more marked, which makes cytology metastases easier to detect. Lorand et al. observed that patients ≤57 years of age presented significantly greater sensitivity and negative predictive value in relation to patients aged over 57 years. Sensitivity was also significantly higher among non-menopausal women in this study, which is probably related to the younger age of these patients[17]. In this study, non-menopausal women presented lower sensitivity than menopausal women, which can be explained by the low number of cases in this group.

In this casuistry, an increase was observed in the sensitivity of ductal carcinomas in lobular carcinomas and, as was the case in most of the literature, these values were not significant[17,24,25]. In 2005, Cox et al., reported a 55.5% sensitivity in ductal carcinomas and 38.7 for lobular carcinomas, in the the detection of lymph node metastases at the intraoperative imprint (p=0.012)[26]. This difference can be explained by the difficulty of intraoperative cytology analysis. According to Turner et al., the loss of e-cadherin results in an individual cell pattern in which metastatic lobular cells appear as small, regular, and round cells, making them difficult to distinguish from normal lymph node cells[17,27].

The intraoperative imprint sensitivity was higher among T3 tumors, although statistical significance was not observed. Zgajnar et al. presented significant values between intraoperative study sensitivity in tumors larger than 10 mm in comparison with those smaller than 10 mm, contraindicating the performance of intraoperative imprint for T1a and T1b tumors, justifying that such finding would occur due to the presence of a greater number of micrometastases in minor tumors[20]. In this study, micrometastasis was observed in an 8 cm tumor and, in 15 cases of T1 and T2 tumors, with a mean tumor size of 2.94 cm.

The sensitivity did not change in relation to the presence of the hormonal receptors. This result was similar to that of Lorand et al., who also did not find significant results[17]. These results can be explained by the association of hormonal receptors with smaller tumors, with lower histological and nuclear grade, and a better prognosis[28].

The presence of neoplastic vascular embolization demonstrated an increase in sensitivity in the sample studied. In a study published in 2011, this relationship was significant (p=0.04)[17]. These findings are explained by the fact that lymph node metastasis is more frequent in the presence of vascular embolism.

In all patients submitted to neoadjuvant chemotherapy (15 cases), the intraoperative imprint cytology was negative. In twelve cases (80%), there was agreement between the imprint cytology and the histopathological study. Only three cases (20%) were positive for the definitive histopathological study and negative for the imprint, two with macrometastasis and one with micrometastasis. Jain et al. evaluated the reliability of imprint in the detection of axillary lymph node metastasis after neoadjuvant chemotherapy and demonstrated a 100% agreement between cytology evaluation and definitive histopathology. Among the 17 patients evaluated in the neoadjuvant group, nine (53%) were positive and eight were negative (47%)[29]. In the study conducted by Miller et al., intraoperative results showed to be in agreement with the final histology in 79% of the patients, demonstrating that the sensitivity of the intraoperative study is not significantly altered by chemotherapy[30].

This study concludes detection of micrometastases with intraoperative imprint is difficult, since the sensitivity is 6.3%, while the sensitivity of macrometastase detection is 73.2% with significant analysis. This is one of the findings presented by Tew et al. in the meta-analysis, in which the mean sensitivity of the detection of micrometastases with the cytology method was 22%, while that of the macrometastases was 81%[21]. Pugliese et al. demonstrated an increase in imprint sensitivity with increased SLN metastasis size, with results equal to 0, 4 and 74%, respectively, in lymph nodes with ITC, micrometastasis and macrometastasis[19]. The data found here were similar to that found by Cox et al., which found sensitivity of 6.4% for micrometastasis and 69.3% for macrometastasis[26].

CONCLUSION

Imprint cytology in the intraoperative examination is a fast, inexpensive method, and does not involve any loss of lymph node tissue that could compromise the definitive histological analysis, as well as showing good accuracy in predicting axillary status. Patient selection based on clinical and histological criteria may improve the sensitivity of the method. However, the only variable that resulted in a significant increase in sensitivity in this study was the presence of macrometastasis.

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POSITIVE PREDICTIVE VALUE OF NONPALPABLE BREAST LESIONS ACCORDING TO BI-RADS® CLASSIFICATION

Valor preditivo positivo das lesões mamárias não palpáveis utilizando a classificação BI-RADS®

Mônica Silva Costa Janson Ney[1], Aline Vargas Goroni[1]*, Giuliana Vasconcelos de Souza Fonseca[1]

ABSTRACT

Introduction: Breast cancer is the neoplasm that most affects women in Brazil and the world, and its incidence has increased steadily over the last decade. Due to screening mammography programs, according to age group, the mortality rate of breast cancer has decreased by 31%. With the increase in the number of screening examinations, there has also been increase in the number of suspicious lesions diagnosed and, consequently, increase in the indication and performance of breast biopsies. With the help of the categorizations that the American College of Radiology published, according to the Breast Imaging Reporting and Data System (BI-RADS®), it was possible to standardize the reports and descriptions of breast lesions, both in mammography and ultrasound, facilitating decision-making in regard to suspicious lesions. **Objective:** To evaluate the positive predictive value (PPV) of nonpalpable breast lesions biopsied in the Radiodiagnostic Service of Hospital Naval Marcílio Dias. **Method:** A retrospective and analytical study of 88 patients submitted to stereotaxic guided mammary biopsies from December 2015 to December 2016 with suspected diagnosis of malignant lesions, classified by mammographic BI-RADS in categories 4 and 5 and later correlation with the histopathological reports. **Results:** PPV was high for category 5 lesions, and for category 4 lesions PPV was low and progressively increased with the subcategories. **Conclusion:** BI-RADS categorization is an effective predictor for the risk of malignancy in suspicious mammographic lesions.

KEYWORDS: Breast cancer; mammography; stereotaxic biopsy; histopathological diagnosis; BI-RADS.

RESUMO

Introdução: O câncer de mama é a neoplasia que mais acomete mulheres no Brasil e no mundo e sua incidência vem aumentando progressivamente ao longo dessa última década. Devido aos programas de rastreamento mamográfico, de acordo com a faixa etária, a taxa de mortalidade por câncer de mama diminuiu em 31%. Com o aumento do número de exames de rastreamento houve aumento, também, da quantidade de lesões suspeitas diagnosticadas e, consequentemente, um aumento na indicação e realização de biópsias mamárias. Com o auxílio das categorizações que o American College of Radiology publicou, segundo o Breast Imaging Reporting and Data System (BI-RADS®), foi possível padronizar os laudos e as descrições das lesões mamárias, tanto na mamografia quanto na ultrassonografia, facilitando a tomada de decisão perante a lesões de aspecto suspeito. **Objetivo:** Avaliar o valor preditivo positivo (VPP) das lesões mamárias não palpáveis nas quais foi realizada biópsia no Serviço de Radiodiagnóstico do Hospital Naval Marcílio Dias. **Método:** Estudo retrospectivo e analítico de 88 pacientes submetidas a biópsias mamárias guiadas por estereotaxia no período de dezembro de 2015 a dezembro de 2016 com diagnóstico suspeito de lesões malignas, classificadas no BI-RADS® mamográfico em categorias 4 e 5, com posterior correlação com os laudos histopatológicos. **Resultados:** Foi encontrado alto valor preditivo positivo na categoria cinco e, nas lesões classificadas como categoria quatro, o VPP foi menor, aumentando progressivamente com as subcategorias. **Conclusão:** A categorização BI-RADS® é um preditor eficaz para o risco de malignidade nas lesões suspeitas na mamografia.

PALAVRAS-CHAVE: Câncer de mama; mamografia; biópsia estereotáxica; diagnóstico histopatológico; BI-RADS®.

Study carried out at Hospital Naval Marcílio Dias – Rio de Janeiro (RJ), Brazil.
[1]Hospital Naval Marcílio Dias – Rio de Janeiro (RJ), Brazil.
***Corresponding author:** linegoroni@gmail.com
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INTRODUCTION

Breast cancer is the cancer that most affects women in Brazil[1] and the second most frequent type of neoplasm in the world. According to statistical studies of the National Cancer Institute (INCA) in Brazil, there are reports of approximately 49,000 cases of breast neoplasm, which are responsible for 12,000 deaths per year[2].

In an estimate made for 2014, and for 2015 as well, 57,120 new cases were predicted, representing an estimated risk of 52 cases per 100,000 women per year. According to data from the Globocan 2012, from the International Agency for Research on Cancer (IARC), the risk accumulated during the lifetime of a person having and dying from breast cancer in Brazil is 6.3% (having) and 1.6% (dying)[3]. In low- and middle-income countries, diagnosis tends to be later in the advanced stages of the disease. In high-income countries, because there is organized population screening, the diagnosis is made when the disease is still in localized stages, resulting in important difference in prognosis and morbimortality.

These data show the importance of cancer control strategies with a set of integrated and systematic measures, aimed at reducing morbidity and mortality. Primary prevention is also contemplated, reducing and eliminating risk factors associated with early detection through mammographic screening.

When diagnosed early, the chances of a better prognosis for breast cancer are higher, thus reducing the morbidity associated with treatment. The recommended screening measures include mammography. Breast self-examination, clinical examination, magnetic resonance imaging (MRI), ultrasound (US), thermography, and tomosynthesis may also be helpful in complementing the diagnosis. The early diagnosis actions proposed by the Ministry of Health include strategies for awareness, identification of signs and symptoms, and diagnostic confirmation in a single service[3]. Screening should occur in women aged 50–59 years with an annual mammogram, and up to 69 years, biennially[3].

There are some signs and symptoms that are considered as an urgent reference for the patient to seek a specialized service, such as nodules in women over 50 years old, nodules that persist for more than one menstrual cycle in women over 30, fixed hard nodule that increases in volume, bloody papillary discharge and retraction of the skin on the breast, among others.

Decrease in mortality rate is closely related to early detection of the disease so that the best therapeutic approach can be taken, with the aim of a better prognosis of the disease. Therefore, effective screening is necessary and mandatory.

The INCA recommends, mainly, self-examination of the breasts and mammography starting at 50 years old. Imaging examinations such as MRI and US also enter into the picture as a complement to screening according to INCA. Thus, awareness strategies, early identification of signs and symptoms and diagnostic confirmation are crucial and indispensable in the fight against breast cancer.

The American College of Radiology (ACR) has released an atlas, the Breast Imaging Reporting and Data System (BI-RADS®), which is in its fifth edition, to promote consistency and uniformity in breast imaging reports, reducing any possibility of confusion in the interpretation of images and facilitating recommendations on taking measures or monitoring. This system unifies mammographic, US and MRI data, standardizing specific findings and classifying them into categories according to each method[4,5].

For the early diagnosis of breast cancer, mammography has been the method with more specificity and sensitivity. Since it is performed periodically, sensitivity varies between 71 and 98%, as analyzed by reviews of the literature[6].

The BI-RADS classification for mammography describes category 0 as those cases with inconsistent findings and that need additional evaluation by other methods or comparison with previous examinations, so the patient would need to be recalled. Category 1 is a negative assessment for normal breasts according to the method, with no probability of malignancy. Category 2 includes benign findings such as cutaneous calcifications, metallic foreign bodies, cysts, implants, etc., also essentially without any likelihood of malignancy. Category 3 classifies those changes with up to 2% probability of malignancy, with probably benign findings, requiring follow-up in six months. To reach a conclusion on the lesions of this category, many studies have shown the safety and efficacy of follow-up by periodic mammograms instead of biopsy. The findings that are validated as probably benign include non-calcified circumscribed solid nodules, focal asymmetry and isolated clustering of punctiform calcifications. BI-RADS itself shows that this category often generates unnecessary follow-up or delay in early diagnosis, showing that even with the standardization of reports, we do not always have an exact science when it comes to disease, and therefore, many studies have confronted these findings.

Findings classified as categories 4 and 5 are those suspicious and highly suspicious of malignancy, respectively, that require histopathological studies to rule out malignancy or detect an early neoplasm. Category 6 changes are already malignant proven by biopsy[6].

In the case of category 4, which are suspicious findings, the risk of malignancy varies between 2 and 95%[6]. These findings are subcategorized as: 4A with low suspicion (2 to 10% probability of malignancy), 4B with moderate suspicion (ranging between 10 and 50%), and 4C with high suspicion for malignancy varying between 50 and 95% chance[6]. This category is reserved for those findings that do not have the classic appearance of malignancy, but are suspect enough to justify recommendation for biopsy.

Category 5 is for mammogram findings at a level of suspicion equal to or greater than 95%.

With the development of BI-RADS in 1993, many studies were conducted to correlate imaging findings with histopathological results, and all were heterogeneous regarding patient selection, histopathological method, and palpable or nonpalpable lesions[7].

In a literature review that evaluated 15 studies, the following results were obtained: positive predictive value (PPV) between 4 and 62% for category 4 (median of 20%) and between 54 and 100% for category 5 (median of 89%), regardless of histopathology method or morphological criteria[7]. It was concluded that mammographic screening for breast cancer, obtaining an early diagnosis, is indisputably responsible for a substantial decrease in mortality due to this disease.

However, with many divergences in radiological findings, many biopsies are performed unnecessarily. Among the studies selected for literature review, many used different methods and some did not mention age nor clinical examination data, making it difficult to compare the data and, therefore, also showed significant differences in the detection of cancer. Only three studies of the 15 evaluated achieved a satisfactory PPV when compared to the PPV suggested by the BI-RADS system.

Another study found that the low PPV in category 4 could be related to the fact that the BI-RADS nomenclature is very comprehensive and not specific, and even to the lack of experience of some radiologists[8].

All studies conclude that there is a great variation in PPV, correlated with the heterogeneity of information collected in each of them, limiting the comparison of results. This, once again, shows the difficulty of establishing a medical standardization to be followed by all specialists, proving that we should always be in search of studies aimed at improving the disease diagnosis pattern.

Also illustrating this importance, another study of clinical relevance reached the conclusion that the histopathological studies of 76% of cases were negative for malignancy and only 24% were positive, showing PPV of 7.14, 16.96 and 82.61% for categories 3, 4 and 5, respectively[9].

Based on these findings, the objective of this study was to determine the PPV of nonpalpable breast lesions that were biopsied at the Radiodiagnostic Service of Hospital Naval Marcílio Dias (HNMD), correlating with the findings of the histopathological studies, and to compare the PPV found with those described in the 5th edition of BI-RADS. We also intended to show the importance of the subclassification of BI-RADS category 4 for radiologists in search of better patient care. It is essential that each service seek to improve its performance in favor of patient care through professional qualification, research incentives, availability of research resources and improvement of diagnostic methods.

METHOD

This study was approved by the Research Ethics Committee of HNMD, and the use of an informed consent form was waived. In this retrospective study, we analyzed all mammograms performed at the Radiodiagnostic Service of HNMD from December 2015 to December 2016 and selected those classified as categories 4 and 5 by BI-RADS, in which patients were subjected to a stereotactic breast biopsy, aiming to demonstrate the agreement of PPV for breast cancer between the 5th edition of BI-RADS classification and histopathological results.

All mammograms were analyzed by radiologists with experience in mammographic diagnosis, and the findings were classified according to the BI-RADS system.

Mammograms evaluated in this study were performed on the Mammomat 3000 Nova mammography machine (Siemens Healthcare, Germany), and the images digitized by the CR-85 X (Agfa HealthCare, São Paulo, Brazil), installed in the mammography and stereotaxy section of the HNMD. The examinations were performed in the craniocaudal and mediolateral oblique views, and complementary views occurred when necessary.

The selected data were obtained from the breast biopsy registry of the mammography section and the computer medical records of the institution, from which the mammogram and histopathological reports were also extracted.

We collected data on patient age and family history of breast cancer, as well as the histological type of cancer in the selected cases.

The inclusion criteria were: patients whose mammogram was classified BI-RADS category 4 and its subdivisions and category 5, and also patients who underwent stereotactic breast biopsy at HNMD.

Patients whose biopsy originated from a mammogram classified as other BI-RADS categories and those who were biopsied at other institutions were excluded from the study.

We selected 88 patients whose cases met the inclusion criteria. The data were organized and tabulated in a Microsoft Excel 2010 worksheet, PPV was calculated using a specific formula, and the final results were compared with BI-RADS 5th edition.

RESULTS

Among the 88 selected cases, the mean age of the patients was 58.61 years old (57.81 years for those with benign histopathology and 60.32 years for those diagnosed with cancer), and the minimum age was 37 and the maximum 85.

In the age group 30 to 40 years, only one had a diagnosis of malignancy out of six cases. Between 41 and 50 years, there were five cases. In the 51 to 60 years group, diagnoses of malignancy totaled eight cases. Between 61 and 70 years, six of the 24 selected cases showed malignancy, and, between 71 and 90 years, there were eight cases of cancer for the 17 biopsies (Table 1).

Of the total of 88 cases analyzed, the percentage distribution of mammographic diagnoses among BI-RADS categories was 94.31% (83) for category 4 and 5.68% (five) for category 5, showing predominance of alterations in category 4. Among the BI-RADS 4 subcategories, there were 20 (22.72%) cases of 4A, 19 (21.59%) of 4B and eight (9.09%) of 4C. Among the 88 cases,

36 were category 4 (40.90%), that is, those patients in which the subcategory was not specified. Table 2 shows the total number of patients and percentages distributed by categories, separating the cases as malignant or benign.

The histopathological results showed 60 patients (68.18%) with a benign result and 28 cases (31.81%) diagnosed as malignant. Of the 28 cases of breast cancer, nine had mammograms classified as category 4 without any subdivision, three as category 4A, seven as 4B and four as 4C, and five cases categorized as 5 (Table 3).

Evaluating only category 4, the 83 cases were subdivided, resulting in 24.09% (20) for subcategory A, 22.89% (19) for B and 9.63% (8) for C. Mammograms categorized as 4, without subclassification, accounted for 43.37%, with 36 cases out of 83 (Table 3).

PPV for category 4 was 27.71%, considering only the 36 exams in which the subcategory was not specified. PPV of the subcategories was 15% for category 4A, 36.8% for 4B and 50% for 4C. PPV for category 5 was 100% (Table 4).

Among the histological types found, infiltrating ductal carcinoma predominated with 57.14% of diagnosed cases of cancer (Table 5).

Although it was not the focus of this study, it was observed that there was predominance of negative family history for breast cancer among the selected patients, even in the most suspicious categories. In those classified as categories 4C and 5, only one patient from each category had a positive family history (Table 6).

DISCUSSION

The BI-RADS classification system was the first attempt to standardize mammographic findings in descriptive terms and it is an important instrument to aid in the suspicion of

Table 1. Number of malignant and benign cases according to age group.

Age (years)	Malignant (n)	Benign (n)	Total (n)
30–40	1	5	6
41–50	5	15	20
51–60	8	13	21
61–70	6	18	24
71–90	8	9	17

Table 2. Percent malignant and benign cases according to BI-RADS category.

BI-RADS	Benign - % (n)	Malignant - % (n)	Total - % (n)
4*	30.68 (27)	10.22 (9)	40.90 (36)
4A	19.31 (17)	3.41 (3)	22.72 (20)
4B	13.63 (12)	7.95 (7)	21.59 (19)
4C	4.54 (4)	4.54 (4)	9.09 (8)
5	0 (0)	5.68 (5)	5.68 (5)

*Examinations in which subcategory was not specified.

Table 3. Percent distribution between subdivisions of BI-RADS category 4.

BI-RADS	Benign - % (n)	Malignant - % (n)	Total - % (n)
4*	32.53 (27)	10.84 (9)	43.37 (36)
4A	20.48 (17)	3.61 (3)	24.09 (20)
4B	14.45 (12)	8.43 (7)	22.89 (19)
4C	4.81 (4)	4.81 (4)	9.63 (8)
Total	72.28 (60)	27.71 (23)	100 (83)

*Examinations in which subcategory was not specified.

Table 4. Positive predictive value of selected mammograms.

Categories and Subcategories	Mammograms (n)	Biopsies positive for malignancy (n)	PPV (%)
4*	36	9	25
4A	20	3	15
4B	19	7	36.84
4C	8	4	50.00
5	5	5	100

*Examinations in which subcategory was not specified; PPV: positive predictive value.

Table 5. Distribution of histological types of cancers diagnosed.

Histological type	n	%
Intraductal carcinoma	4	14.28
Infiltrating ductal carcinoma	16	57.14
Infiltrating carcinoma	1	3.64
Invasive carcinoma	7	25

Table 6. Distribution of cases with positive (+) or negative (-) family history.

BI-RADS	(+)	(-)	Total
4*	3	33	36
4ª	4	16	20
4B	4	15	19
4C	1	7	8
5	1	4	5

*Examinations in which subcategory was not specified.

malignancy and in the measures to be taken. Associated with this classification, there was also progressive increase in the number of biopsies.

In the present study, 31.81% of mammograms in which a biopsy was done for histopathological examination showed malignancy, that is, the overall PPV was 31.81%. In the United States, this value varies between 15 and 40%[9-13].

Some studies correlated mammographic and histopathological findings of breast lesions found a PPV for breast cancer between 12.3 and 47.8%[8,14-16]. BI-RADS suggests values above 95% for category 5, and we obtained PPV of 100% in mammograms with this category. The 100% PPV for category 5 is within the range expected from the several cases cited in the literature, in which the values range from 54 to 100%[13-24].

In the literature, mammographic sensitivity is described as greater than 90%, although it has limited specificity, and between 65 and 90% of all biopsied mammary lesions are benign[23,24].

In category 4, the chance of malignancy is between 2 and 95%[5] according to BI-RADS, and PPV is between 2 and 10% in subcategory 4A, between 10 and 50% in 4B, and between 50 and 95% in 4C. In this study, we found PPV of 27.71% for category 4, and in the literature it varies between 4 and 63%. On the other hand, PPV calculated separately for subcategories showed for subcategories 4A, 4B and 4C values of 15, 36.8 and 50%, respectively.

Here, we did not take into account the radiological findings of the selected cases, but, in the experience of this service, microcalcifications are the most commonly biopsied findings using stereotactic guidance.

Malignancy cases in this study predominated in the age ranges of 51 to 60 and 71 to 90, in which the most frequent histological type was infiltrating ductal carcinoma followed by invasive carcinoma, and most cases collected had no positive family history.

With the data found, we observed that the BI-RADS classification allows us to safely predict that there are high suspicion for malignancy in category 5-classified lesions and progressive decrease in suspicion in the lower categories.

In category 4, the percentage variation between the subdivisions is very large, but we can see progressive increase in PPV given to the subclassifications A, B and C, showing that this subdivision contributes, in a more detailed and precise way, to the indication of suspicious lesions, making it necessary to perform systematic biopsies.

This study demonstrated that we should look more and more at the findings of mammographic lesions, always seeking to take into account the BI-RADS category and subcategory, so that we can provide greater assurance for patients and the attending physician.

CONCLUSION

This study showed that the BI-RADS categorization is an effective predictor for the risk of malignancy in suspicious mammographic lesions.

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BREAST CANCER IN THE HEALTH INSURANCE SYSTEM OF JUNDIAÍ: DATA ON 105 PATIENTS

Câncer de mama no sistema de saúde suplementar de Jundiaí: dados de 105 pacientes

Rodrigo Gregório Brandão[1,2]*, Joaquim Teodoro de Araújo Neto[1], Gil Facina[1]

ABSTRACT

Introduction: The data related to breast cancer's epidemiology in Brazil are heterogenous, reflecting the country's socioeconomic inequalities. Significant number of cases of this disease are attended through the health insurance system, but data on these cases is poorly disseminated. **Objective:** To evaluate epidemiological data on breast cancer from patients attended through the health insurance system in the municipality of Jundiaí, São Paulo. **Methods:** This was a retrospective study conducted through reviewing the medical files of 105 patients diagnosed with breast cancer, who were attended between January 2014 and December 2015. The information gathered included: age, clinical staging, histological type, immunohistochemical profile, surgical treatment and adjuvant treatment. **Results:** The study included 105 patients with breast cancer who were treated exclusively within the health insurance system of Jundiaí. The patients' mean age was 50.8 years. We observed that 13 patients (12.3%) were diagnosed with ductal carcinoma *in situ* (stage 0), 43 (40.9%) with stage I, 34 (32.3%) with stage II, 11 (10.4%) with stage III and 2 (1.9%) with stage IV. Conservative surgery was performed on 76 patients (72.3%), while 29 (27.7%) underwent mastectomy. Among the latter, immediate reconstruction was performed in 82.7% (24) of the cases. **Conclusion:** The high rates of early diagnosis and conservative surgery show that screening for breast cancer within the health insurance system of the municipality of Jundiaí, has been effective. Accessible mammography and the socioeconomic level of the population seem to be the main factors responsible for the obtained findings.

KEYWORDS: Breast neoplasms; supplemental health; mastectomy; mammography; epidemiology.

RESUMO

Introdução: Os dados referentes à epidemiologia do câncer de mama no Brasil são heterogêneos, reflexo da desigualdade socioeconômica do país. A medicina suplementar possui número relevante de casos da doença, porém estes são pouco divulgados. **Objetivo:** Avaliar os dados epidemiológicos do câncer de mama em pacientes atendidas pela saúde suplementar no município de Jundiaí, SP. **Método:** Estudo retrospectivo por meio da revisão do prontuário médico de 105 pacientes com diagnóstico de câncer de mama atendidas entre janeiro de 2014 e dezembro de 2015. As informações coletadas incluíram: idade, estadiamento clínico, tipo histológico, perfil imuno-histoquímico, tratamento cirúrgico e adjuvante. **Resultados:** O estudo incluiu 105 pacientes com câncer de mama, tratadas exclusivamente no sistema de saúde suplementar de Jundiaí. A idade média das pacientes foi de 50,8 anos. Observamos que 13 (12,3%) pacientes foram diagnosticadas com carcinoma ductal *in situ* (estádio 0), 43 (40,9%) no estádio I, 34 (32,3%) no estádio II, 11 (10,4%) no estádio III, e 2 (1,9%) no estádio IV. A cirurgia conservadora foi realizada em 76 (72,3%) pacientes, das quais 29 (27,7%) foram submetidas à mastectomia. Nessas pacientes, a reconstrução imediata foi realizada em 82,7% (24) dos casos. **Conclusão:** A elevada taxa de diagnósticos precoces, assim como de cirurgias conservadoras, revela rastreamento eficaz para o câncer de mama na saúde suplementar do município de Jundiaí. A acessibilidade à mamografia e o nível socioeconômico da população parecem ser os principais responsáveis pelos achados obtidos.

PALAVRAS-CHAVE: neoplasias da mama; saúde suplementar; mastectomia; mamografia; epidemiologia.

Study carried out at Women's Healthcare Unit, Breast Clinic – Jundiaí (SP), Brazil.
[1]Discipline of Mastology, Department of Gynecology, Escola Paulista de Medicina, Universidade Federal de São Paulo – São Paulo (SP), Brazil.
[2]Women's Healthcare Unit, Breast Clinic – Jundiaí (SP), Brazil.
***Corresponding author:** rodrigobrandao.masto@gmail.com
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INTRODUCTION

Jundiaí is a city with approximately 400,000 inhabitants[1]. It has been calculated that 60% of its population has access to some type of health insurance plan[2]. This proportion is quite above the national average (23%) and the average for the state of São Paulo (44%)[2]. The high coverage of health insurance in this municipality leads to the supposition that this is an important factor within the epidemiological data relating to the population's health.

Breast cancer is the most frequent malignant disease among women, except for non-melanoma skin cancer. One in every ten tumors diagnosed worldwide occurs in breast tissue, and this is the largest cause of death due to cancer among the female Brazilian population[3]. Unfortunately, the rates of early diagnosis and timely treatment in Brazil remain insufficient. Despite important advances over the last two decades, the overall five-year survival rate is only around 58%, which is below the global average (61%) and the averages of countries like Costa Rica (70%) and the United States (84%)[4].

The Brazilian epidemiological data reflect the enormous socioeconomic heterogeneity of its population, which in the regions of temperate climate (south and southeast) present rates close to those of European countries, while in the northern states data are similar to those of central African countries[5].

Healthcare strategies and policies need to be based on very clear epidemiological data. Determining the regions in which mammographic screening is insufficient and where there are difficulties regarding its coverage and delays in starting treatments, it is vital for improving healthcare. Longitudinal incidence and mortality data may define the course of actions and reveal the obtained results. On the other hand, cross-sectional data presents the situation at a given moment in time and provides information on clinical staging, subgroups that are at greater risk and the types and frequencies of implemented treatments, among other matters. There are no efficient actions without the interpretation of essential information.

PATIENTS AND METHODS

This retrospective descriptive cross-sectional study was developed based on the revision of the medical files of 105 patients who were diagnosed with breast cancer between January 2014 and December 2015. They were attended at the Women's Healthcare Unit — Breast Clinic (a private medical center), in the municipality of Jundiaí, SP. All of them underwent operations performed by the same breast surgeon. All of them were assisted through a health insurance system.

The information gathered included: age, clinical staging (TNM; AJCC 7th ed), histological type, immunohistochemical profile, surgical treatment (conservative versus radical, with or without immediate reconstruction) and adjuvant treatment.

Descriptive statistical methods were used, and the results were demonstrated by graphs and tables. The data were stored and tabulated using the Microsoft Excel software.

RESULTS

The study included 105 patients with breast cancer who were treated exclusively through the health insurance system in Jundiaí. Patients' mean age was 50.8 years, with a range from 21 to 86 years; 79 patients (75%) were up to 60 years and 25 (23%) of them were under 40 years (Figure 1).

The distribution of patients among health insurance companies was as follows: 65.7% (69 patients) with Unimed; 12.3% (13 patients) with Bradesco; 5.7% (6 patients) with Amil; and 16.1% (17 patients) with other plans.

Regarding staging, we observed that 13 patients (12.3%) were diagnosed with ductal carcinoma *in situ* (stage 0), 43 (40.9%) with stage I, 34 (32.3%) with stage II, 11 (10.4%) with stage III and 2 (1.9%) with stage IV. 61 patients (58%) were diagnosed with tumors smaller than 2.0 cm. Seventy-six patients (71.4%) presented local disease (affecting breast and axilla), 28 (26.6%) regional disease (involving breast and axilla) and only two (2%) presented systemic disease at the time of diagnosis (Figure 2).

Non-special invasive carcinomas (formerly known as invasive ductal carcinoma) were responsible for 75.2% of the cases, followed by ductal carcinoma *in situ* in 12.3% of the cases, invasive lobular carcinoma (7.6%) and special carcinomas, 3.8%. Regarding molecular subtypes, it was observed that 27 (25.7%) were classified as luminal A, 31 (29.5%) as luminal B, 5 (4.7%) as luminal-HER, 3 (2.8%) as subtype HER 2+ and 10 (9.5%) as triple negative. For 29 cases (27.6%) no immunohistochemical study was available.

Conservative surgery (quadrantectomy) was performed on 76 patients (72.3%), while 29 (27.7%) underwent mastectomy. These latter cases were divided into two groups, namely:

- total mastectomy, 19 cases;
- subcutaneous mastectomy, 10 cases (Figure 3).

Among all 105 patients included in the study, 50 (47.6%) underwent immediate breast reconstruction procedures. The most performed method was oncological mammoplasty, in 26 cases.

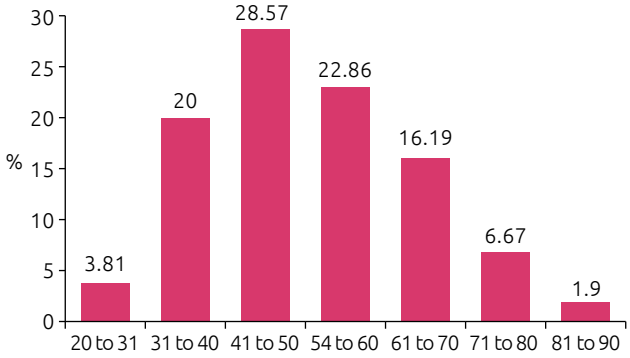
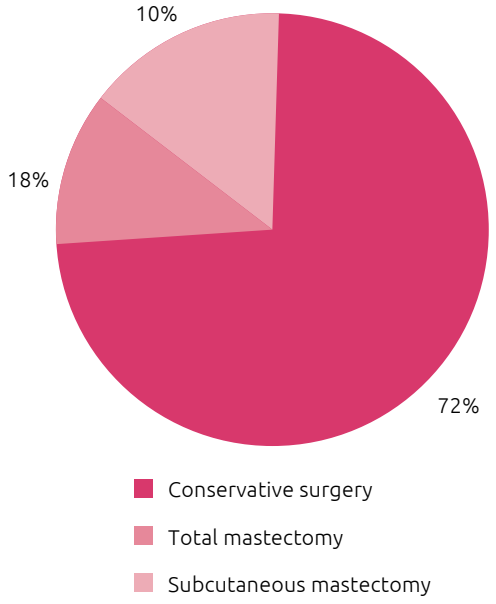


Figure 1. Patients' ages at the time of receiving their diagnosis of breast cancer at the breast clinic (health insurance system in the municipality of Jundiaí), between January 2014 and December 2015 (n=105) (%).

This term is used for techniques in which the breast volume and/or the excess skin is reduced after conservative surgery, and it needs to include measures to achieve symmetry in relation to the contralateral breast. Reconstruction using definitive implants was performed in 16 patients, using temporary expanders in five and definitive in three. Myocutaneous flaps wasn't used in any case for immediate reconstruction.

Figure 2. Distribution of patients with breast cancer attended at the breast clinic (health insurance system in the municipality of Jundiaí), according to their clinical stage.



O.M.: oncological mammoplasty.

Figure 3. Distribution of surgical procedures performed on the patients with breast cancer treated at the breast clinic (health insurance system in the municipality of Jundiaí), between January 2014 and December 2015 (n=105) (%).

Among the 105 patients analyzed, 60 (57.1%) underwent chemotherapy. The type of regimen and the endocrine therapy used were not analyzed in this study.

DISCUSSION

Brazilian epidemiological data related to breast cancer are scarce and scattered. They depend to a large extent on cross-sectional data published by centers and care services in different regions of the country. Most of the data come from university services and synthetize the national public healthcare panorama[6]. Some authors have analyzed data on breast cancer from the health insurance system and observed that the situation was favorable. The data presented in this study reveal the epidemiological profile of the region and makes it possible to formulate proposals in order to adapt resources and optimize the screening and treatment results for breast cancer in the municipality of Jundiaí, SP.

It should be noted that 23% of the patients were diagnosed with breast cancer at ages under 40 years. This figure is much greater than what has been observed in other samples. In the United States, only 6.6% of cases were under this age[7], 5% in Canada and 4% in the United Kingdom[8]. Other studies in Brazil found rates between 9.8 and 12.1%[9,10]. The reason for these results remains unclear. The population attended by the health insurance system in Jundiaí has an age distribution similar to that of the municipality's general population. Data released by Unimed Jundiaí demonstrate that among their patients over 20 years of age, 53.3% are between 20 to 40 years. For the entire population of the municipality, this number is 48%[1]. Moreover, the incidence of breast cancer among young women remains stable. Differing from the rates among patients over 40, the incidence of breast cancer among women has been stable over the last 30 years[11].

Regardless of the reasons, the figures demonstrate that there are many patients with breast cancer at young ages. This draws attention to the possibility that hereditary genetic syndromes might be present and signals that there is a need to preserve the fertility of those patients who might still want to be pregnant.

The evaluation of the 105 patients demonstrated that 71% of them received their diagnosis at an initial stage of the disease (i.e., when the disease was limited to the breast). These data were superior to what was found in countries such as the United States (58.6%)[12] and Canada (68%)[13]. Most of Brazilian data has solely revealed the public healthcare scenario. The Brazilian Group for Breast Cancer Studies (GBECAM) has compiled epidemiological information on staging at the time of diagnosis among patients in both public and private systems of Brazil[14]. They observed that 20% of the diagnoses were in stages 0 and 1. However, in public system, only 15% of the patients received their diagnosis in these stages, while in private system 33% did so. Other published data covering patients solely within Brazilian public system emphasized that the proportion of the diagnoses at the initial stages

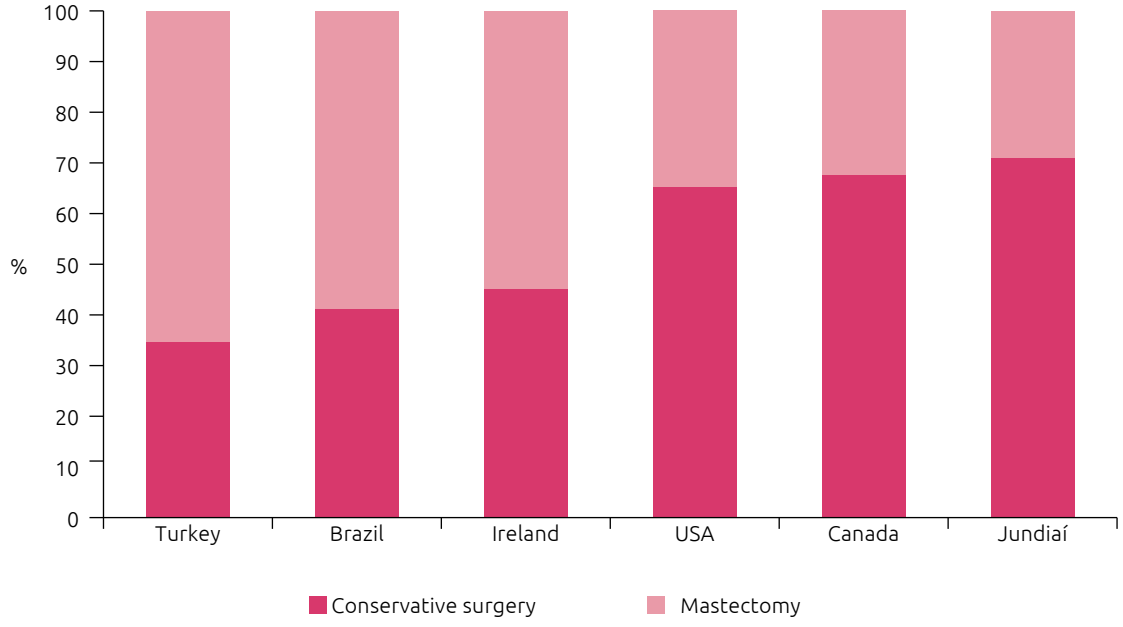
was always lesser than 20%[15]. The data from the present study revealed that 53.1% of the diagnoses were made in stages 0 and 1.

Early diagnosing of breast cancer depends fundamentally on three variables: availability of mammography, access to healthcare services and population's socioeconomic level. Data from the United States have demonstrated annual differences in incidence and mortality rates due to breast cancer in different ethnic and socioeconomic groups. This incidence is greater among white population and in states with a higher human development index (HDI), while mortality rates due to breast cancer are higher in Afro-descendant and Latin populations, especially in groups of lower socioeconomic level. Today, Jundiaí has an estimated population of 400,000 inhabitants, with the highest HDI among Brazilian major cities. The health insurance system has five mammograph machines, i.e., more than World Health Organization's recommendation (one machine per 100,000 inhabitants). Thus, the data of the present study describes an epidemiological scenario of breast cancer in a high socioeconomic level population, with mammography available and an accessible healthcare system. This association of factors is responsible for the high rate of early diagnosis observed.

From an epidemiological point of view, surgical treatment for breast cancer says much about the status of a given country in relation to combating this disease. High numbers of mastectomies correspond to late diagnosis and possibly represent overtreatment. This situation involves higher expenditure, complication rates, morbidity and sequelae for the patients. The benefit of conservative surgery is beyond esthetic issues. It enables faster physical and emotional recovery, with lower cost and, especially, fewer sequelae. In turn, survival seems to be greater than in cases of mastectomy, possibly because of the benefit of radiotherapy[16]. It was observed that 76 patients (72.3%) underwent quadrantectomy, while 29 (27.6%) underwent mastectomy. Data from GBECAM revealed that in 2008, 68% of the patients attended within Brazilian public healthcare system (SUS) underwent mastectomy, while 50% of them underwent this procedure among the patients attended through the private system. In China, this number was 78%[17]. In countries like the United States and Canada, the figures are inverted, such that mastectomy is used in approximately 30% of the cases[12,13] (Figure 4).

Breast reconstruction rates in Brazil are unknown. Only some reports from university hospitals are available. Although Brazilian healthcare policies guarantee full access to treatments for cancer, the conditions for implementing this policy are insufficient. Since 2012, there have been laws that specify that all Brazilian citizens with malignant neoplasia have the right to receive treatment within 60 days, from when the diagnosis is made (Federal Law no. 12.732/12), as well as the right to breast reconstruction for those who undergo either conservative or radical surgery (Federal Law no. 12.802/13)[15]. The health insurance system in Jundiaí follows the determinations of the National Agency for Supplemental Healthcare (ANS) and covers for all breast reconstruction procedures, including those with use of prostheses.

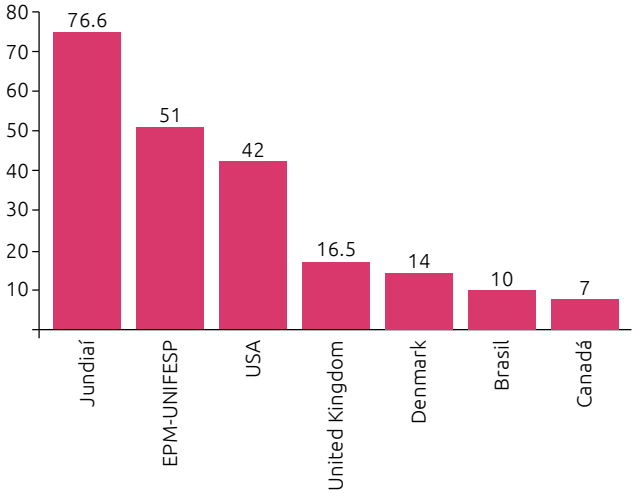
The data presented reveal that 47.6% of the patients underwent breast reconstruction. Repair techniques following quadrantectomy were most frequently used. In the literature, there is little information on the statistics related to this form of treatment, given that no healthcare systems around the world consider this to be obligatory. Reconstruction techniques following



Source: National Cancer Registry, Ireland[15]; SIH, DataSUS[16]; Canadian Institute of Health Information[17]; American Cancer Society[18]; Breast Cancer in World and Turkey, Prof. Dr. Vahit Özmen[19].

Figure 4. Relation between conservative surgery and mastectomy for treating breast cancer observed in different regions (%).

mastectomy are well known[17-19] (Figure 5). In Escola Paulista de Medicina (UNIFESP), the rate of reconstruction following mastectomy was 51% between 2014 and 2015[20]. Reconstruction is performed according to the patient's desire, as well as to her clinical condition. Published data show that women with higher schooling level, high socioeconomic level and age under 60 years are the group that is most likely to undergo this procedure[21-24]. In turn, the clinical conditions that contraindicate reconstruction include: tumors compromising skin, presence of metastases (multiple and with a poor prognosis) and significant clinical morbidity.



Source: adapted from SIH, DataSUS, 2010[16], Platt et al.[18], Howard-McNatt[19], EPM – UNIFESP 2014 and 2015[23].

Figure 5. Breast reconstruction rates after mastectomy in different regions of the world (%).

CONCLUSION

The presented data demonstrate the importance of early diagnosis for breast cancer and show its repercussions on this disease's treatment. Awareness, both among doctors and their patients, is fundamental for the results observed. Strategies for combating mortality due to malignant diseases depend especially on epidemiological information. Thus, this study presents the need for future efforts towards registering and publishing data on diagnosis and treatment of breast cancer in Brazil, not only from patients within public healthcare system but also from those within the private one.

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CASE REPORT
DOI: 10.29289/2594539420180000330

USE OF THORACOEPIGASTRIC FLAP IN LARGE BREAST RESECTIONS: PHYLLODES TUMOR CASE REPORT

Utilização do retalho tóraco-epigástrico em grandes ressecções da mama: relato de caso de tumor filoide

Douglas de Miranda Pires[1], Guilherme Junqueira Souza[1]*, Bárbara Pace[1]

ABSTRACT

Phyllodes tumors are uncommon fibroepithelial breast neoplasms capable of displaying a diverse range of biological behaviors. In their less aggressive form, they behave as benign fibroadenomas, although with a propensity to local recurrence after excision with satisfactory margins. On the other hand, they can metastasize, sometimes degenerating histologically into sarcomatous lesions. Phyllodes tumors represent less than 0.5% of all breast pathologies. They are smooth, multinodular, well-defined, firm, mobile, and painless masses of variable sizes, which can reach 40 cm in large tumors, with bright and stretched skin. When they progress to large tumor masses, they become a challenge to mastologists who need surgical satisfaction and coverage of the resected area. The use of thoracoepigastric flap has been an important surgical tool for these large breast lesions. The present study describes a case report of a large malignant phyllodes tumor that used the thoracoepigastric flap for coverage and closure.

KEYWORDS: Phyllodes tumor; surgical flaps; breast neoplasms.

RESUMO

Os tumores filoides são tumores de mama fibroepiteliais incomuns capazes de uma gama diversificada de comportamentos biológicos. Em sua forma menos agressiva, comportam-se como fibroadenomas benignos, embora com uma propensão a recorrer localmente após a excisão com margens satisfatórias. Por outro lado, podem metastatizar, algumas vezes, degenerando histologicamente em lesões sarcomatosas. Os tumores filoides representam menos de 0,5% de todas as patologias mamárias. Apresentam-se como uma massa lisa, multinodular, bem definida, firme, móvel e indolor, de tamanho variável, podendo chegar a 40 cm em grandes tumores, com a pele brilhante e esticada. Quando evoluem a grandes massas tumorais, tornam-se um desafio ao mastologista que necessita da satisfação cirúrgica e cobertura da área ressecada. A utilização do retalho tóraco-epigástrico tem sido uma importante ferramenta cirúrgica para essas grandes lesões da mama. O presente estudo apresenta o relato de caso de um tumor filoide maligno de grande volume, utilizando-se do retalho tóraco-epigástrico para cobertura e fechamento.

PALAVRAS-CHAVE: Tumor filoide; retalhos cirúrgicos; neoplasia da mama.

Study conducted at Santa Casa de Belo Horizonte – Belo Horizonte (MG), Brazil.
[1]Clínica de Mastologia, Santa Casa de Belo Horizonte – Belo Horizonte (MG), Brazil.
***Corresponding author:** guilhermejunqueirasouza@gmail.com
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INTRODUCTION

Phyllodes tumors are rare lesions, with an incidence of less than 1% of all breast tumors, more frequent among white women aged 35 to 55 years. Clinically, they are most commonly presented as a rounded, mobile, painless nodule of fast growth. Histologically, these tumors are biphasic lesions with epithelial and stromal components[1].

The classification of the World Health Organization (WHO) of 2003 proposed cataloging phyllodes tumors into three categories (benign, borderline, and malignant), according to the degree of cellular atypia, mitotic activity, characteristics of tumor margins, and stromal growth[2]. Phyllodes tumors grow fast; however, when small, it is difficult to differentiate them from fibroadenomas. Characterizing malignant forms is also problematic due to their large cellularity and atypia variation, making broader samples necessary for a conclusive diagnosis[3]. The treatment for phyllodes tumors is surgical removal. For tumors with borderline or malignant filaments, or in cases of local recurrence, mastectomy can become the preferred option. The role of adjuvant treatments is not proven and should be considered on a case by case basis. Patient follow-up is necessary due to the risk of local and distant metastases. Patients submitted to mastectomy with significant tissue loss will certainly need a quick and safe procedure that ensures the closure of the deformity area, aiming at the coverage and survival of the flap.

Faced with these challenges, the mastologist should count with the maximum number of surgical techniques that provide surgical correction and satisfaction. This text is dedicated to the use of thoracoepigastric flap in large closures, for being a resolutive, viable, and effective procedure.

The Reference Center for Women's Health of Hospital Pérola Byington, in São Paulo, analyzed all consecutive patients who underwent radical mastectomies between 2009 and 2014, and had chest wall reconstructions, having the viability of the flap and effectiveness of the surgical closure as outcome, with locally advanced breast tumors and resection area ranging from 13 to 20 cm. Out of the 29 patients, only two had wound dehiscence, which was handled without new approach[4].

The flap is drawn across the thoracoabdominal region ipsilateral to the thoracic lesion, parallel to the mammary fold. The base of the flap is positioned medially from the xiphoid process to the midpoint between the latter and the umbilicus. The lateral limit is the posterior axillary line with the patient in supine position. The lateral edge of the flap must be rounded for better use[4].

Other series show studies with a small number of patients, but with satisfactory results.

METHODS

This is the clinical case report of a patient with a large malignant phyllodes tumor, surgically treated with the thoracoepigastric flap technique. The patient was assisted by the mastology team of Santa Casa de Belo Horizonte, associated with the public health system (*Sistema Único de Saúde* – SUS).

CLINICAL CASE

The patient I.R.R was 24 years old and had her first appointment at the mastology center of Santa Casa de Belo Horizonte on April 19, 2017. She presented a voluminous mass in the right breast, stretching across the skin. The patient was being monitored by another service in the North of Minas Gerais since 2011 due to a nodule in the right breast (breast ultrasonography on March 22, 2011: 35 × 17 × 35 mm) with Fine-Needle Aspiration Biopsy (FNAB) resulting in fibroadenoma. In 2014, she underwent the first surgical intervention, with excision of the nodule, classified as fibrosclerotic stroma with no signs of malignancy. In 2015, new breast nodules with progressive growth and varying sizes were found, the major one having 6 cm in its largest axis. She underwent a new surgical approach with an anatomopathological result of benign phyllodes tumor, without atypia, with metaplasia areas and free margins. In 2016, the follow-up breast ultrasonography showed four other nodules (1; 1.2; 1.4, and 4.2 cm), leading to a new biopsy in February 2017. The result was fibroadenoma, complemented with immunohistochemical (ER+, PR-, E-cadherin-, HER2-, Ki-67 [35%]), which detected a benign phyllodes tumor. In April 2017, she visited our unit complaining of an exaggerated increase in breast size after the last biopsy and for surgical excision of the lesions.

As per protocol, the patient received the Informed Consent Form (ICF) and had pictures taken for pre-, intra-, and postoperative evaluating purposes (Figures 1, 2, 3, 4, 5, 6, 7, and 8). The approach chosen was mastectomy with reconstruction using thoracoepigastric flap and, on May 12, 2017, the patient

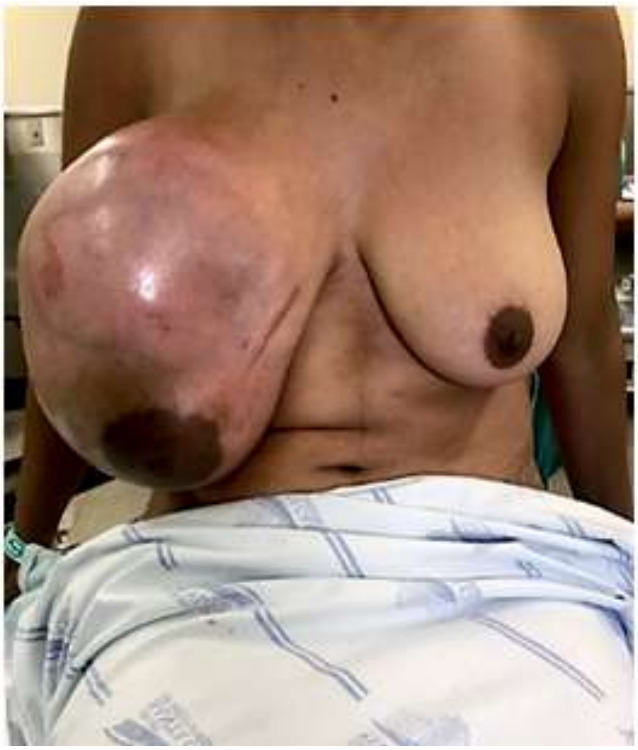

Figure 1. Preoperative.

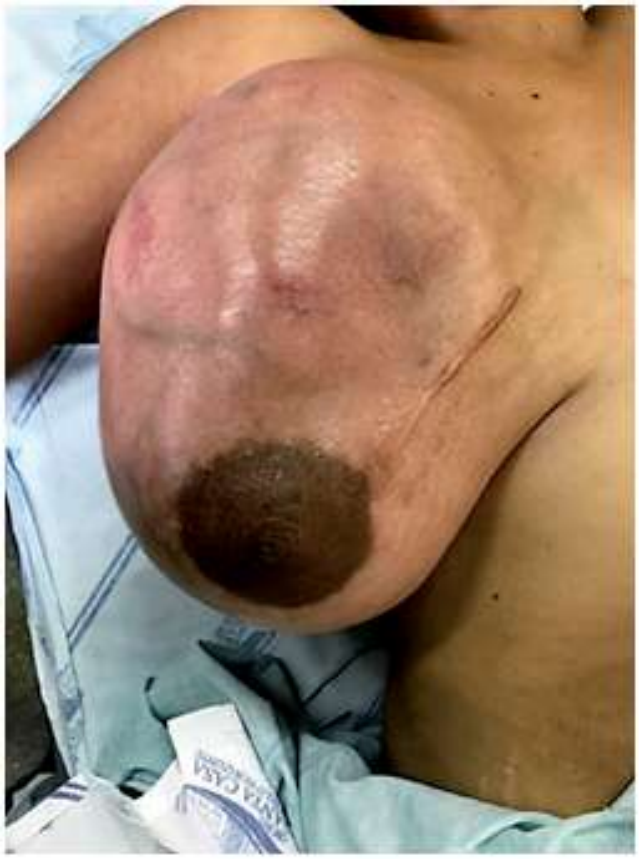

Figure 2. Preoperative: right unilateral view.

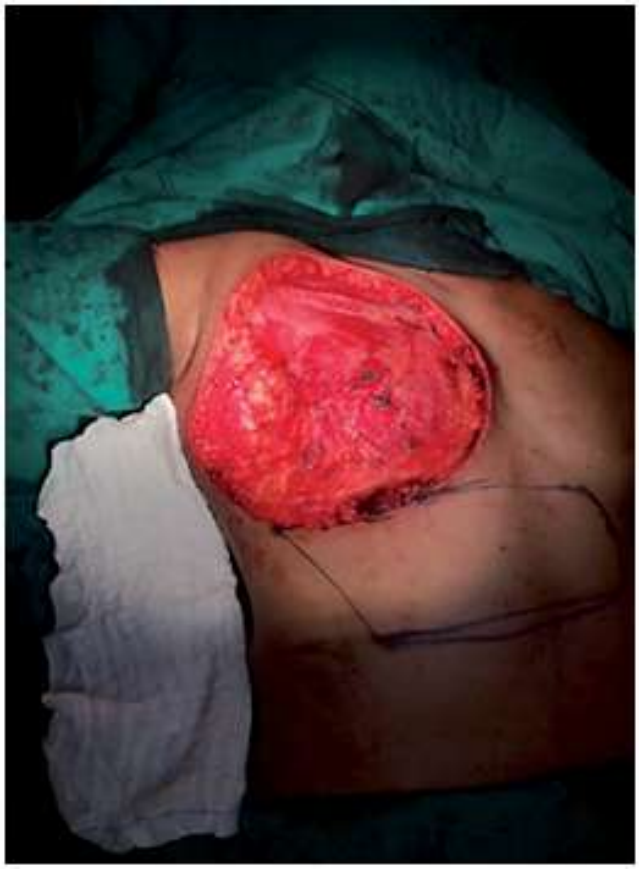

Figure 3. Mastectomy resection area.

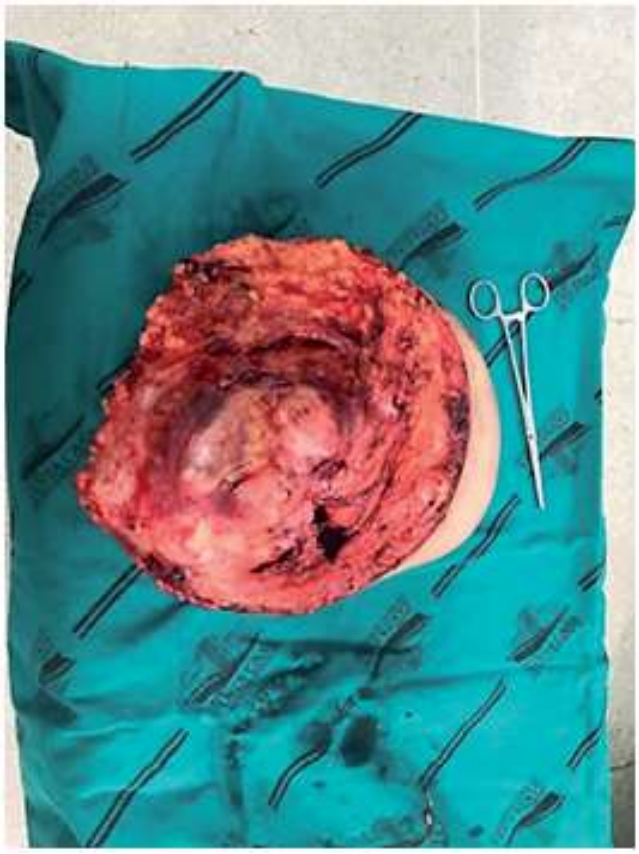

Figure 4. Surgical specimen resulting from mastectomy.

Figure 5. Thoracoepigastric flap preparation and synthesis.

underwent surgical treatment. The deformity area was repaired preserving a 1.5:1 ratio and the anatomical limits, as recommended by the literature[5]. Axillary drainage was performed due to lymphadenopathies identified in the intraoperative period, without complications.

In the postoperative follow-up, the drains and local curative were removed with mineral oil, without flap-related complications, keeping a good aspect and with good healing progress.

The patient was monitored weekly without changes from a surgical point of view, and the anatomopathological evaluation identified a malignant phyllodes tumor of high degree, narrow posterior margin (1 mm), and reactive lymphoid hyperplasia. She was referred for clinical oncology and radiotherapy evaluation, which opted for a clinical and mastology follow-up only.

Up to the present date, she is in a quarterly follow-up, with no signs of locoregional recurrence. The technique proved to be quite versatile, with satisfactory oncological outcomes, providing a good closure of large resection areas, without damage to the donor site.

DISCUSSION

Phyllodes tumors are uncommon fibroepithelial neoplasms, representing less than 0.5% of breast tumors, with a mean onset in

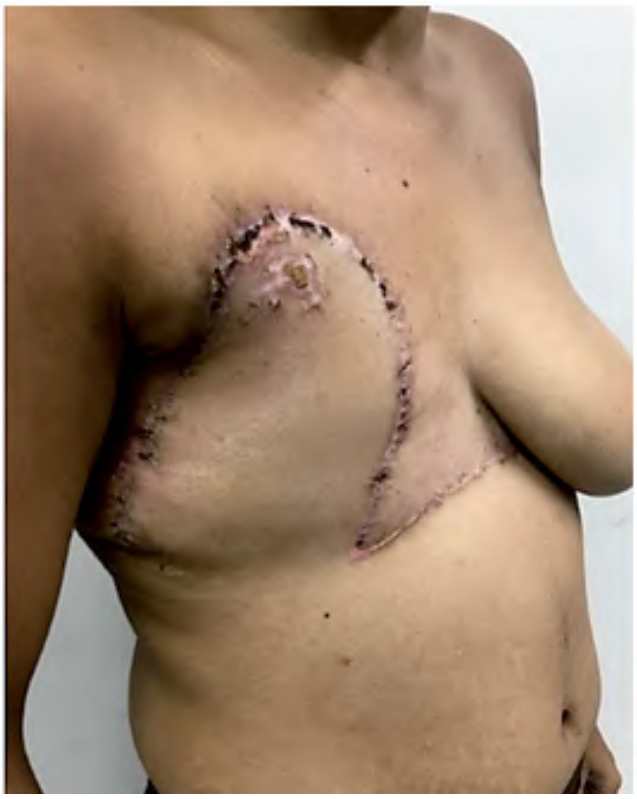

Figure 7. Thirty days after the postoperative.

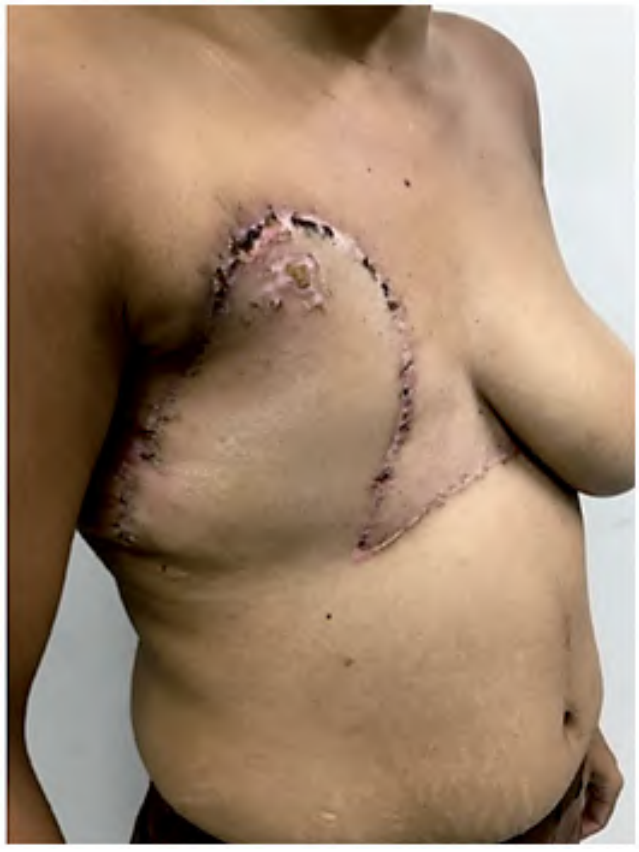

Figure 6. First postoperative week.

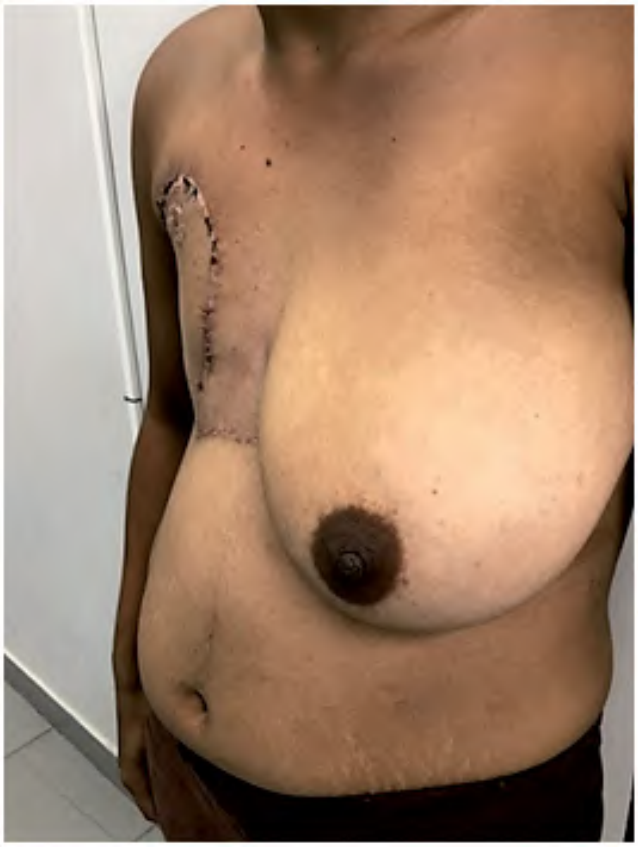

Figure 8. Thirty days after the postoperative: left oblique view.

the fourth decade of life[6]. Usually, they are large, solid, multinodular, well-defined, and mobile masses of variable sizes, and those of large volume present a thinning of the skin.

Mammography detects approximately 20% of these lesions and should be complemented with ultrasonography[7]. In general, the lesions should be punctured (FNAB) or subjected to Core Biopsy (CB).

Surgical treatment should aim at a safety margin due to the high recurrence rate of these lesions. A multivariate analysis, which included 172 patients with phyllodes tumors, associated positive surgical margin with an almost four times higher risk of a tumor-related event, such as local recurrence or metastasis (HR=3.9, 95%CI 1.1–14.3)[8]. Currently, the literature recommends margins larger than 1 cm.

Axillary drainage should not be considered and is restricted to selected cases, as the greater spread is hematogenous and most axillary lymph nodes are reactive. A study with data from the Surveillance, Epidemiology, and End Results Program of the USA indicated only eight among 498 women with affected axillary lymph nodes[7].

Considering these variants, the mastologist must be prepared for the surgical approach. There is no consensus on which technique is the best to use, however, for large resections, the thoracoepigastric flap becomes a great tool for breast surgeons, as it is technically easy to perform, secure, and presents low morbidity.

The objective of this work was to make the use of oncoplastic techniques, such as thoracoepigastric flap, a practice applicable to the daily routine of surgeons. As in the case report, lesions that leave large chest wall deformities become resectable and have good closure.

Thoracoepigastric flap results in lower morbidity, shorter length of hospital stay, and low complication rates in the donor site when compared to myocutaneous flaps[5].

FINAL CONSIDERATIONS

In many situations, large breast tumors with unfavorable tumor/breast ratio, associated with the histological type and clinical conditions, lead the mastologist to decide for mastectomies involving large resections. Over time, the involvement and qualification of mastologists in oncoplastic techniques improved the surgical arsenal, considering methods that are easy to perform and targeted at each patient. Currently, the thoracoepigastric flap is an important surgical tool for the closure of large chest wall deformities, with lower morbidity and complications.

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CASE REPORT
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METAPLASTIC BREAST CARCINOMA IN A PREGNANT WOMAN: CASE REPORT

Carcinoma metaplásico da mama em uma gestante: relato de caso

Jocela Cristina dos Santos[1], Andrea Tatiane Oliveira da Silva[2], Marta Maria Vasconcelos de Araújo[3], Caroline Carvalho Ferro[3], Raiana Santos Lins[4]*

ABSTRACT

Breast cancer is the most common malignant neoplasm diagnosed during pregnancy. Metaplastic carcinoma is a rare type of breast cancer, representing 1.5% out of all kinds. This is a case report of metaplastic carcinoma in a pregnant woman aged 39 years.

KEYWORDS: Breast cancer; pregnancy; mastectomy, modified radical.

RESUMO

O câncer de mama é a neoplasia maligna mais comumente diagnosticado durante a gestação. O carcinoma metaplásico é um tipo raro de câncer mamário que representa 1,5% de todos os tipos. A seguir, é relatado um caso de carcinoma metaplásico em gestante de 39 anos.

PALAVRAS-CHAVE: Câncer de mama; gestação; mastectomia radical modificada.

[1]Hospital do Açúcar – Maceió (AL), Brazil.
[2]MedRadius – Maceió (AL), Brazil.
[3]Hospital Universitário Professor Alberto Antunes – Maceió (AL), Brazil.
[4]Universidade Federal de Alagoas – Maceió (AL), Brazil.
***Corresponding author:** linsraiana@gmail.com
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INTRODUCTION

Breast cancer is the most common malignant neoplasm diagnosed during pregnancy[1]. Its incidence is approximately 1 in every 3 thousand pregnancies[2,3]. Metaplastic breast carcinoma is a rare type of tumor that represents 0.25 to 1.5% out of all kinds of breast cancer[1,4,5]. The 5-year survival rate is around 49 to 68%[5]. Usually, this neoplasm is a palpable breast mass in women older than 50 years[4]. The present work is a case report of metaplastic breast carcinoma in a pregnant woman aged 39 years.

CASE REPORT

E.L.S., 39 years old, G2P1A0, 23 weeks of gestational age. She visits the oncology surgery unit complaining of hyperemia in the right breast, as well as itching and a fast-growing nodule in the prior month. The patient reported a history of fibroadenoma in the right breast in the past year, followed by the mastology department. She had a positive family history of breast cancer (mother with the first tumor at 39 years old and second at 68 years old). She denies smoking and other comorbidities. The examination revealed a tumor in the right breast of approximately 10 × 8 cm and palpable lymph nodes in the right axilla. Breast ultrasonography showed a heterogeneous nodular image, with anechoic and solid echogenic areas, vascularization on Doppler, measuring approximately 10.3 × 7.1 × 8.8 cm, located at the upper outer quadrant of the right breast, with close contact with the skin and deep muscle planes, classified as BI-RADS US 4C (Figure 1). The axillary investigation identified lymph nodes of normal aspect, with the largest measuring 1.1 × 0.6 cm. The core biopsy of the lesion detected a poorly differentiated invasive breast carcinoma (variant of squamous cells – grade III). Other requested laboratory tests were within normal limits. The treatment chosen was modified radical mastectomy with lymph node dissection, adjuvant chemotherapy, and, after delivery, radiotherapy. Histopathological examination of the surgical specimen (16 × 11.5 × 6 cm) (Figure 2) revealed metaplastic carcinoma with a predominance of squamous cell carcinoma, moderately differentiated, without vascular invasion, free margins, and lack of lymph node metastasis in the 37 lymph nodes resected. The chemotherapy regimen chosen was anthracycline, cyclophosphamide, and taxane.

DISCUSSION

Pregnancy-related breast cancer includes those diagnosed during pregnancy or up to one year after delivery. Breast cancer detected during the first trimester of pregnancy limits the treatment options, delaying chemotherapy until the second trimester, as the fetus is at lower risk in this stage[1]. Breast cancer during pregnancy is associated with a worse prognosis, both for the diagnosis in more advanced stages and the limitation on chemotherapy and radiotherapy treatment due to the risk of fetal malformation[1]. Surgery is the treatment of choice and can be conducted in all trimesters of pregnancy. Modified radical mastectomy is the preferred approach since radiotherapy for breast conservation cannot be administered[3]. Metaplastic breast carcinoma (MBC) is defined as a mixture of epithelial and sarcomatoid components, can be histologically classified as purely epithelial or mixed epithelial and mesenchymal[4,6], and is the most common squamous cell carcinoma[6]. Imaging tests presented characteristics similar to invasive ductal carcinoma and benign lesions, with mammography showing irregular or circumscribed masses with spiculated area and ultrasonography indicating a heterogeneous cystic mass[4,6]. MBC is characterized by a large fast-growing mass, often triple-negative for estrogen, progesterone, and HER2 receptors[1,4]. Less than 20% of cases are hormone receptor positive[7,8]. It has a greater chance of hematogenous than lymphatic metastasis, with axillary lymph node involvement ranging from 8 to 40% of cases, and presents a high rate of systemic metastasis[4,7,9], being more common in the

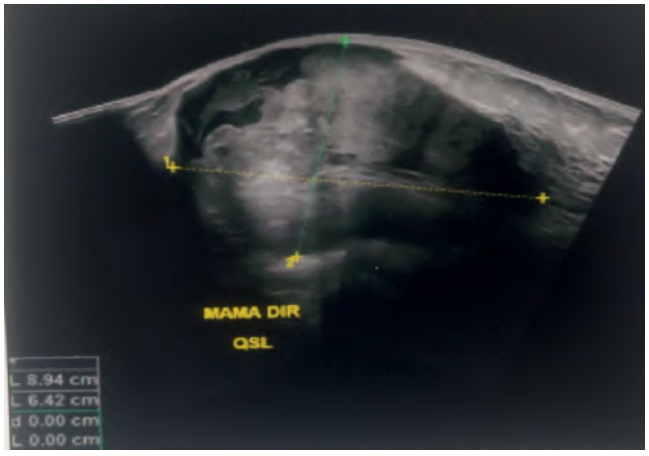

Figure 1. Right breast ultrasonography showing heterogeneous nodular image.

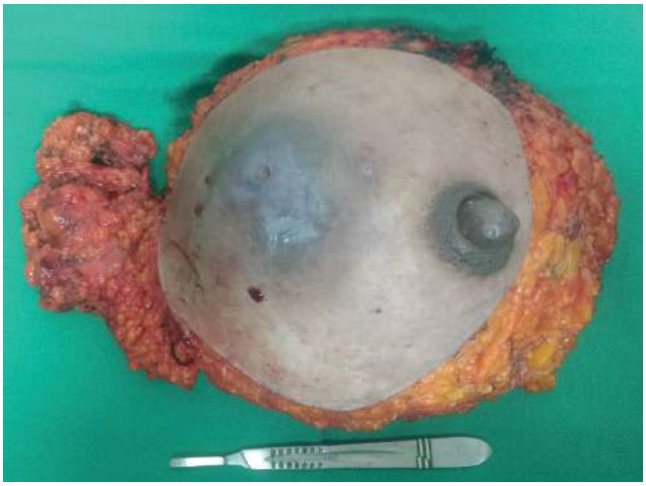

Figure 2. Surgical specimen (right breast).

lungs, brain, thyroid, chest wall, and abdominal cavity. Local recurrence occurs in approximately 8 months to 5 years after lesion excision[7]. Onset before 40 years of age, skin invasion, and lymph node involvement are predictors of poor prognosis[4,6]. In the case reported, the patient presented predictors of poor prognosis, such as being 39 years old and skin involvement; however, she did not have lymph node metastasis. A study by Rakha et al. showed that the squamous, fusiform, and mixed fusiform subtypes have a worse prognosis. In the present work, the histopathological diagnosis revealed a predominance of the squamous cell subtype[5]. A study conducted in Saudi Arabia by Altaf et al. identified MBC in two pregnant women — one of them with a recent history of abortion — out of seven patients. Their immunohistochemistry presented cells morphologically similar to syncytiotrophoblasts, indicating choriocarcinomatous differentiation, with more aggressive behavior[10]. There is no consensus on the ideal treatment for MBC; however, surgery with axillary staging and chemotherapy has been currently adopted. Radiotherapy is also indicated when the tumor is larger than 5 cm or has more than four lymph node metastases[1,4]. Rakha et al. found that chemotherapy is associated with better outcomes, despite having effect limited to cases in initial stages[5]. The literature has extremely limited data on neoadjuvant chemotherapy, making it impossible to establish what their results would be[8]. Taxane-based chemotherapy has shown good results[6]. In a study conducted in 2015, Aydiner et al. verified that adjuvant radiotherapy improved patient survival[9,11]. In the case reported, the treatment chosen was modified radical mastectomy with lymph node dissection, as the patient could not undergo radiotherapy for breast preservation due to her pregnancy, even with a tumor larger than 5 cm. In addition, the tumor extension did not leave margins to perform conservative surgery and presented palpable axillary lymph nodes. Besides the surgery, the patient underwent adjuvant chemotherapy, since she was already in the second trimester of pregnancy, and radiotherapy after deliver due to the large tumor size.

CONCLUSION

Breast cancer during pregnancy has shown worse prognosis due to limitations on the use of radiotherapy and chemotherapy because of the risk of fetal malformation. Thus, the treatment of choice is surgery and chemotherapy after the second trimester, with the preferred approach being modified radical mastectomy. In this population group, metaplastic breast carcinoma has a high incidence, particularly the squamous cell subtype. The image shows a fast-growing heterogeneous cystic mass, with a higher chance of hematogenous metastases, particularly to the lungs, brain, thyroid, chest wall, and abdominal cavity. It is important to promptly diagnose and treat MBC due to its aggressive nature, capable of rapid growth and systemic metastasis. We should try to preserve the integrity of the fetus by adopting less aggressive treatments and waiting for a lower risk period to start more effective therapies. However, the ultimate goal is the maternal treatment.

The authors declare that the patient allowed publication of the case after signing the Informed Consent Form (ICF).

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CASE REPORT
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FOREIGN BODY IN THE BREAST: MULTIPLE SEWING NEEDLES

Corpo estranho no parênquima mamário: múltiplas agulhas

Leonardo Ribeiro Soares[1], João Wesley Cabral Moura-Filho[1], Katyane Larissa Alves[1], Regis Resende Paulinelli[1], Ruffo Freitas-Junior[1]*

ABSTRACT

Needles embedded in the breast are an unusual situation. It is reported the possibility of developing an abscess and the risk of migration of the needles. We report the case of a 38 year old woman with approximately 25 needles inserted in her breasts, bilaterally. According to the patient, the insertion occurred during the episode of a recent physical aggression; however, the hypothesis of self-mutilation could not be ruled out. She also referred the withdrawal of some needles at home and tried a surgical resection of others. Physical examination of the breasts revealed bilateral bruising, located in the upper inner quadrant of the left breast and diffusely in the right breast. Ultrasound examination showed needles in both breasts, associated with a hyperechoic area between 5 and 6h of the right breast, corresponding to palpable clinical area. An X-ray and chest tomography also revealed the presence of several needles in the breasts. At mammography, multiple intra-mammary needles and lymph nodes were diffusely distributed through the parenchyma, bilaterally. After discussing with the patient about the diagnosis and therapeutic options, we opted for clinical follow-up. Currently, the patient has moderate acyclic mastalgia, and is on clinical follow-up for 55 months.

KEYWORDS: Breast; mammography; foreign bodies; needles.

RESUMO

Agulhas inseridas no parênquima mamário constituem uma situação incomum, podendo haver ocorrência de abscessos e o risco de migração das agulhas. Descrevemos o caso de uma paciente do sexo feminino, de 38 anos de idade, diagnosticada com aproximadamente 25 agulhas de costura em suas mamas, bilateralmente. Segundo a paciente, a inserção ocorreu durante episódio de agressão física recente; porém, a hipótese de automutilação não pôde ser descartada. A paciente também referiu a retirada domiciliar de algumas agulhas e a tentativa de retirada em outro Serviço. Ao exame físico das mamas, evidenciava-se equimose bilateral, localizada no quadrante súpero-medial da mama esquerda e difusamente na mama direita. O exame ultrassonográfico evidenciou agulhas em ambas as mamas, associadas à área hiperecoica entre 5 e 6h da mama direita, correspondente a área clínica palpável. A radiografia e a tomografia de tórax visibilizaram a presença de vários corpos estranhos nas mamas, de aspecto metálico, compatíveis com agulhas. Após discussão com a paciente acerca do diagnóstico e das opções terapêuticas, optou-se por conduta expectante. Após 55 meses, a paciente refere mastalgia acíclica moderada e mantém seguimento clínico no Serviço.

PALAVRAS-CHAVE: Mama; mamografia; corpos estranhos; agulhas.

[1]Gynecology and Obstetrics Department, Program of Mastology, Universidade Federal de Goiás – Goiânia (GO), Brazil.
***Corresponding author:** ruffojr@terra.com.br
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Female patient, 38 years old, rural worker, with bipolar mood disorder, former smoker and with a family history of breast cancer (maternal aunt). The patient reported a recent physical aggression, with approximately 25 needles inserted in her breasts, bilaterally. However, the hypothesis of self-mutilation could not be ruled out. She referred the withdrawal of some needles at home and tried a surgical resection of others.

Physical examination of the breasts revealed bilateral bruising, located in the upper inner quadrant of the left breast and diffusely in the right breast. The lesions presented areas associated with hyperemia, bilaterally, and palpable thickening in the lower quadrant of the left breast (Figure 1).

Ultrasound examination showed needles in both breasts, associated with a hyperechoic area between 5 and 6h of the right breast, corresponding to palpable clinical area. An X-ray and chest tomography also revealed the presence of several needles in the breasts. At mammography, multiple intra-mammary needles and lymph nodes were diffusely distributed through the parenchyma, bilaterally (Figures 2 and 3). To our knowledge, this is the first report of multiple needles diagnosed in mammary parenchyma, bilaterally. In similar cases described in the literature[1,2], the recommendation of surgical removal due to the risk of abscesses and needle migration is highlighted[1-3]. However, the large number of needles and the technical difficulty for the individual removal of each one makes bilateral mastectomy the most appropriate surgical technique. After discussion with the patient about the diagnosis, the risks and therapeutic options, we opted for clinical follow-up. Currently, the patient has moderate acyclic mastalgia, and is on clinical follow-up for 55 months.

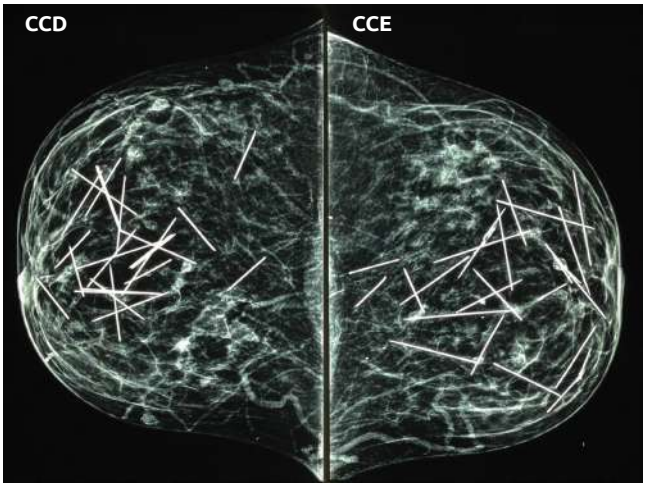

Figure 2. Mammography, craniocaudal view. Multiple intra-mammary needles were diffusely distributed through the parenchyma, bilaterally.

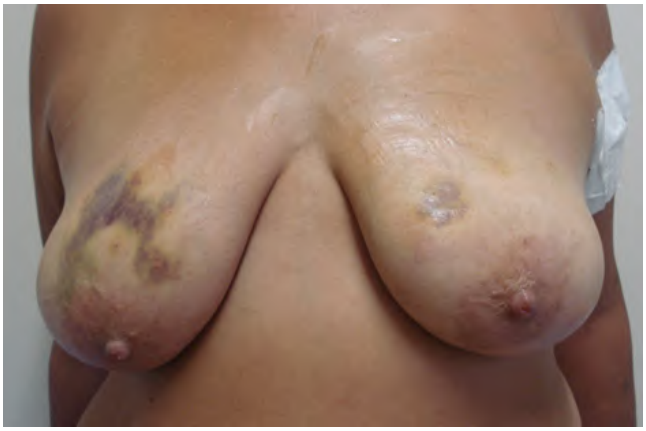

Figure 1. Breast examination at the time of the first visit to the Service. The patient had bilateral ecchymosis, located in a upper inner quadrant of the left breast and diffusely in the right breast.

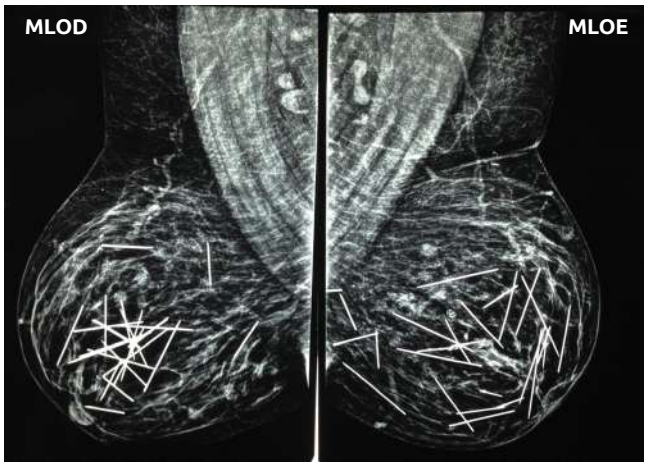

Figure 3. Mammography, mediolateral oblique view. Multiple intra-mammary needles were diffusely distributed throughout the parenchyma, bilaterally.

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CASE REPORT
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WHEN THE INTRAMAMMARY LYMPH NODE IS THE SENTINEL: A CASE REPORT

Quando o linfonodo intramamário é o sentinela: relato de um caso

Karla Sorandra Felipe de Oliveira[1]*, Francisco Pimentel Cavalcante[1,2,3]

ABSTRACT

Sentinel lymph node biopsy is currently well established in the assessment and determination of axillary status in breast cancer patients. In this scenario, finding intramammary lymph node are not uncommon, but the intramammary sentinel lymph node is rare and has uncertain therapeutic and prognostic significance, which may create difficulties in the management of these patients. Reports in the literature show a worse prognosis when the intramammary sentinel lymph node is compromised by metastasis, because at least 60% of these cases will have concomitant axillary disease. However, the decision on axillary dissection must be determined by the first drainage to the axilla, i.e. by the axillary sentinel node, and when this is not identified, axillary dissection should be recommended due to failure of the method. We report a case of intramammary sentinel lymph node identified and isolated during surgery by the Mastology Service of the General Hospital of Fortaleza, and an updated review of available literature on this subject.

KEYOWRDS: Sentinel lymph node; sentinel lymph node biopsy; lymphatic metastasis; lymph nodes; breast cancer.

RESUMO

A biópsia do linfonodo sentinela está atualmente bem estabelecida na avaliação e na determinação do *status* axilar em pacientes com câncer de mama. Nesse cenário, o achado de linfonodo intramamário não é raro, porém o linfonodo sentinela intramamário é raro e tem significado terapêutico e prognóstico incertos, podendo assim criar dificuldades no manejo dessas pacientes. Relatos na literatura mostram pior prognóstico quando o linfonodo sentinela intramamário for comprometido por neoplasia, pois pelo menos 60% desses casos terão doença axilar concomitante. Contudo, a decisão sobre a dissecção axilar deve ser determinada pela primeira drenagem para a axila, ou seja, pelo linfonodo sentinela axilar, e quando este não for identificado, o esvaziamento axilar deve ser recomendado por falha do método. Reportamos aqui um caso de linfonodo sentinela intramamário identificado e isolado durante cirurgia pelo serviço de Mastologia do Hospital Geral de Fortaleza, e uma revisão atualizada da literatura disponível sobre essa temática.

PALAVRAS-CHAVE: Linfonodo sentinela; biópsia de linfonodo sentinela; metástase linfática; linfonodos; câncer de mama.

[1]Hospital Geral de Fortaleza – Fortaleza (CE), Brazil.
[2]Comissão do Título de Especialista, Sociedade Brasileira de Mastologia – Rio de Janeiro (RJ), Brazil.
[3]Comissão de Oncoplastia, Sociedade Brasileira de Mastologia – Rio de Janeiro (RJ), Brazil.
***Corresponding author:** karlasorandra@hotmail.com
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INTRODUCTION

The local treatment of breast cancer has undergone great evolution in the last decades. Sentinel lymph node biopsy(SLNB) to determine axillary status is an example: currently, axillary dissection is avoided even when the SLN has limited metastatic disease [1,2].

Finding intramammary lymph nodes in mammography exams is not uncommon, however it is uncommon in the intramammary sentinel lymph node (ISLN), especially when there is no identification of axillary SLN, its therapeutic meaning or controversial prognosis.

We present a case report of a patient with ISLN, identified and isolated during surgery by the Mastology Service of the General Hospital of Fortaleza (HGF), after informed consent and authorization from the Ethics Committee, under number 2,646,759.

CASE REPORT

An 82-year-old female patient sought the HGF Mastology service reporting the appearance of a right breast nodule, discovered during self-examination three months prior. The patient had systemic hypertension as a comorbidity, controlled with oral antihypertensive medication. An irregular, painless nodule measuring 2.5 × 2.0 cm was identified during the physical examination. There were no palpable axillary lymph nodes. A mammogram examination revealed irregular asymmetry in the upper quadrant of the right breast, corresponding to the palpable area, as well as axillary lymph nodes and one ipsilateral intramammary lymph node.

An ultrasound-guided biopsy was performed, and an invasive grade II carcinoma was diagnosed without other specifications. Immunohistochemistry revealed negative hormone receptors, superexpressed human epidermal growth factor receptor 2 (HER2) and a 40% Ki 67 cell proliferation index. Sectorectomy surgery and SLN biopsy were scheduled.

The preoperative, intradermal and periareolar injection with the radiopharmaceutical (technetium-99) was performed, followed by lymphoscintigraphy, which identified two axillary SLNs and one ISLN (Figure 1).

After excision of the tumour site, the SLNs were identified with the aid of a gamma probe, resected and analyzed intraoperatively by frozen biopsy. Mammary carcinoma metastasis were found in two axillary lymph nodes and one intramammary lymph node via longitudinal sections, which were all confirmed in the definitive histology. The surgical margins of the mammary area were free. Due to the capsular extravasation of an axillary sentinel ganglion, a level 1 axillary dissection was performed, with histopathology showing six metastases free lymph nodes.

After the patient recovered from the surgery, adjuvant radiotherapy was commenced without intercurrences. Systemic therapy with chemotherapy and target therapy (trastuzumab) was not used due to the patient's age and co-morbidities

The patient had 83 months of follow-up, with no signs of local or distant recurrence.

DISCUSSION

The SLN is the gold standard for determining axillary status and its application has been consolidated in recent years. Initial contraindications, such as lesions greater than 3.0 cm, multicentric, biopsies or previous surgeries, gestation, among others, have declined over the years, and today there are practically no limitations to its use. However, the identification of ISLNs can create difficulties in the management of patients, since its clinical, therapeutic and prognostic significance is uncertain and controversial.

The incidence of intramammary lymph nodes is quite variable, and are more commonly found in the lateral quadrants of the breast. They are considered normal in the mammography exam when they are well defined, round or oval, with radioluscent centers and smaller than 1 cm. However, is the identification of these lymph nodes important before surgery? In a study of 93 specimens containing intramammary lymph nodes, 23 were identified preoperatively, metastasis was more frequent (43%) when the lymph node was identified by previous imaging[3]. However, the majority of these lymph nodes will be negative for the the presence of cancer, with positivity varying between 24 and 34% of cases [3,4].

There are some publications in the literature on positive ISLNs and their implications, with reports of worse prognosis, shorter disease-free interval and survival in general [5,6]. After identifying axillary ISLNs and SLNs in 15 patients, Intra et al. concluded that axillary status should be determined by axillary SLNs, and when axillary SLNs were not identified, axillary dissection should be recommended due to failure of the method [7].

A retrospective review of pathology findings demonstrated that intramammary lymph nodes were evident in only 2% of

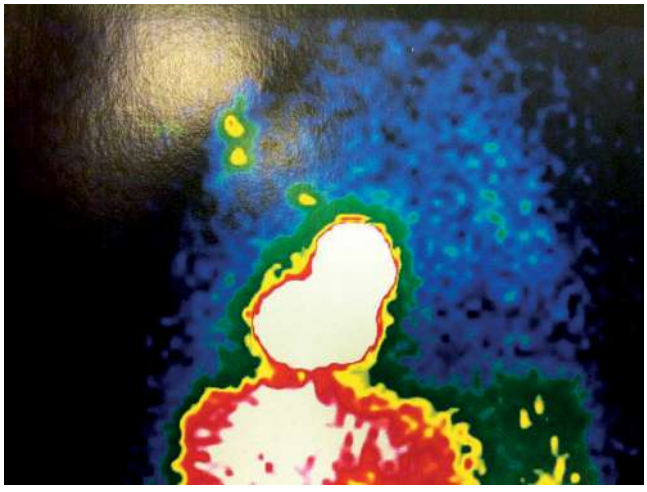

Figure 1. Lymphoscintigraphy with an intramammary sentinel lymph node and two axillary sentinel lymph nodes.

the cases, with positive lesions being less uncommon. However, axillary disease was identified in 61% of the cases with metastasis of these lymph nodes, and no additional axillary disease was found when the axillary SLN was negative and the intramammary lymph node was simultaneously compromised, suggesting that axillary dissection should be based on axillary SLN findings[8] Our patient presented with a detected and metastatic ISLN, in addition to two compromoised axillary SLNs, with one capsular extravasation. These findings corroborate with the literature, suggesting a greater risk of axillary involvement in cases with positive ISLNs. Our positioning on axillary dissection was facilitated by the presence of nodal extravasation in the axillary SLN.

The decision about radiotherapy or systemic therapy can also be a reason for debate in this scenario. The axillary lymph node is an important prognostic marker, and according to most guidelines, adjuvant therapy is recommended when it is metastatic. A retrospective review showed that patients with only compromised ISLNs have a better prognosis when compared to positive axillary SLN alone. In this study, it was also observed that the ISLN does not necessarily predict the axilla: in eight women with positive ISLNs, none had axillary involvement[9]. These data suggest that the impact of ISLN is less than that of the axillary, but it does not mean that it is irrelevant, as there are reports of more association with more aggressive cancer due to increased angiolymphatic invasion and axillary metastasis[10].

CONCLUSION

We conclude that our case coincides with findings in the literature which report poor axillary prognosis when there is a ISLN compromised by neoplasia. The decision on axillary dissection should be determined by the first drainage to the axilla, i.e. the axillary SLN. However, more data are needed to define the importance of ISLN in axillary status, as well as deciding on additional therapies.

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CASE REPORT
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RARE POSTPARTUM PRIMARY NECROTIZING FASCIITIS OF THE BREAST FOLLOWING MASTECTOMY: CASE REPORT

Fasciíte necrosante primária de mama rara no período pós-parto seguida de mastectomia: relato de caso

Luiz Murillo Lopes de Britto[1], Maryane Chagas Barboza Brasilino[2], Thazio Henrique Soares Cardoso de Souza[2], Michelly Nóbrega Monteiro[1], Suzelle Freitas de Moura Oliveira[1], Ricardo Ney Cobucci[3]*

ABSTRACT

Primary necrotizing fasciitis (NF) of the breast is extremely rare. It progresses rapidly and can lead to sepsis and multi-organ failure without prompt medical and surgical management. Herein we describe the case of a healthy 42-year-old woman on the 10th day after cesarean section, who was admitted to the intensive care unit (ICU) with a painful and swollen right breast. It evolved rapidly in the ICU into septic shock and nipple discharge. She underwent immediate resuscitation followed by muscle-sparing right mastectomy. She was managed postoperatively in the ICU with intravenous antibiotic therapy. Complications included acute renal failure and anuria, leading to death on the fourth day after surgery. Prompt resuscitation and an aggressive surgical approach are critical to the successful management of this life-threatening pathology. Despite this, NF still carries a high mortality rate.

KEYWORDS: Breast; fasciitis, necrotizing; sepsis; mastectomy.

RESUMO

A fasciíte necrosante primária (FN) da mama é extremamente rara. Ela progride rapidamente e pode levar à sepse e à falência de múltiplos órgãos sem pronto atendimento médico e cirúrgico. Aqui descrevemos o caso de uma mulher saudável de 42 anos de idade no décimo dia pós cesárea, que foi admitida na unidade de terapia intensiva (UTI) com a mama direita dolorida e inchada. O quadro evoluiu rapidamente na UTI a choque séptico e descarga mamilar. Ela foi submetida a ressuscitação imediata seguida de mastectomia de mama direita com preservação muscular. Foi administrada terapia endovenosa com antibióticos na UTI durante o período pós-operatório. Complicações incluíram insuficiência renal aguda e anúria, levando à morte no quarto dia após a cirurgia. A reanimação imediata e uma abordagem cirúrgica agressiva são fundamentais para o sucesso do manejo dessa patologia que é ameaçadora. Apesar disso, a FN ainda carrega uma alta taxa de mortalidade.

PALAVRAS-CHAVE: Mama; faciite necrosante; sepse; mastectomia.

Study carried out at the Maternidade Escola Januário Cicco – Natal (RN), Brazil.
[1]Maternidade Escola Januário Cicco, Universidade Federal do Rio Grande do Norte – Natal (RN), Brazil.
[2]Universidade Federal do Rio Grande do Norte – Natal (RN), Brazil.
[3]Gynecology and Obstetrics Department, Universidade Potiguar – Natal (RN), Brazil.
***Corresponding author:** rncobucci@unp.br
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INTRODUCTION

Necrotizing fasciitis (NF) is a surgical diagnosis characterized by friability of the superficial fascia, a notable absence of pus, and dishwater-gray exudate[1]. Developing in the lower or upper extremities, in the abdominal wall, the perineum and genital area, its swift clinical course is correlated with polymicrobial infection and synergy, which usually co-exist and rarely affects the breast[2,3].

Necrotizing infections can occur after major traumatic injuries, as well as after varicella infection, non-penetrating soft-tissue injuries, minor breaches of the skin or mucosa, or routine obstetrical and gynecologic procedures; they can also occur in postsurgical and immunocompromised patients[1].

Although it can occur at any site on the body, NF of the breast is extremely rare. It was first described in the literature by Shah et al.[4] in 2001, and only a handful of cases have been published since then[5]. We present a case of primary NF of the breast in a healthy 42-year-old female patient.

CASE REPORT

A 42-year-old woman underwent cesarean section 10 days before, after a diagnosis of preeclampsia (gravida 2, para 2). She subsequently went to the clinic with a complaint of fever, chest pain and a painful and swollen right breast. It was dyspneic, with diffuse hyperemia and edema in the right breast; there was an axillary temperature of 39 degrees Celsius and oxygen saturation of 90% in ambient air.

Due to the dyspneic condition with low saturation, she was medicated with intravenous dipyrone and tenoxicam and transferred to the Emergency Department of a tertiary hospital.

On examination at this new hospital, there was an increased volume of her right breast with infectious signs (Figure 1), heart rate of 104 beats per minute, blood pressure of 80/60 mmHg, oxygen saturation of 97% under Venturi mask, auscultation with a crackle in the right base and abdomen with a clean surgical wound, without signs of infection, painless and flaccid. Due to the hypothesis of puerperal mastitis with sepsis, the patient was admitted to the intensive care unit (ICU).

The patient arrived at ICU complaining of intense right breast pain, torporous, tachypneic, with a respiratory rate of 33 incursions per minute, axillary temperature of 33.8 degrees Celsius, heart rate of 120 beats per minute and blood pressure of 94 / 57 mmHg. Due to her condition, she was submitted to orotracheal intubation and material was collected for arterial gasometry, uroculture, blood culture and breast tissue culture (Table 1). In addition, volume expansion with analgesia, intravenous antibiotic therapy with ceftriaxone, oxacillin and clindamycin were initiated and the evaluation of mastology and breast ultrasonography was required. On the second day in ICU, the patient evolved with a lowering of consciousness level, oliguria, acidosis, with a hardened and swollen right breast. Ultrasound revealed a diffuse and subcutaneous edema, a thick content forming a small collection in one of the medial quadrants, estimated at 28 mm, which may represent an inflammatory / infectious process.

The mastologist then decided on surgical intervention and a right mastectomy was performed (Figure 2). The anatomopathological study revealed absence of neoplasia, extensive areas of vascular congestion and tissue hemorrhage, stromal fibrosis and extensive acute mastitis (Figure 3). In the immediate postoperative period, the antibiotic regimen was changed to cefepime, vancomycin and clindamycin, but the condition worsened, with cyanosis of extremities, anuria, acute renal failure and septic shock resulting in patient's death on the fourth day after surgery.

DISCUSSION

Necrotizing fasciitis (NF) is a rare but aggressive soft tissue infection most commonly affecting the abdominal wall, perineum and extremities, being rare in the breast. It is characterized by widespread fascial necrosis with relative sparing of skin and muscle; it occurs more commonly in patients with comorbidities such as alcoholism, immunocompromise, intravenous drug use and diabetes mellitus. Streptococcus pyogenes is the most commonly implicated organism and it is cultured in approximately one

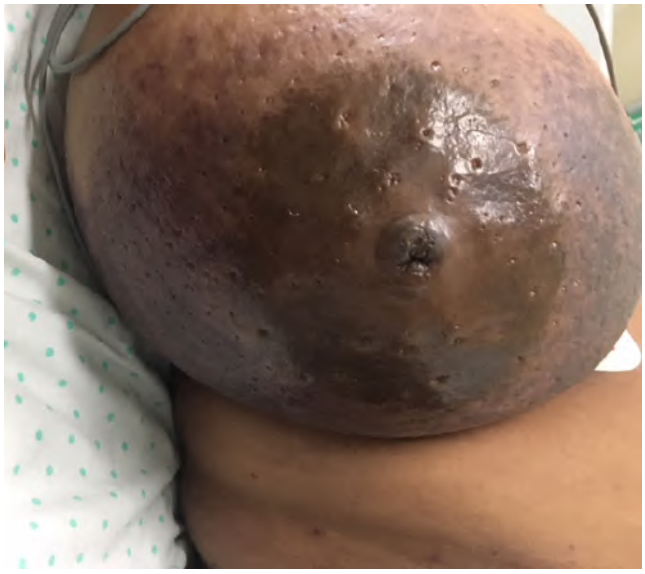

Figure 1. Frontal view of affected right breast.

Table 1. Intensive care unit (ICU) exams.

Exam	Results	Reference values
Arterial gasometry	pH=7.18 pCO_2=25.85	pH 7.35–7.45 pCO_2 35–45
Uroculture	Negative	Negative
Blood Culture	Negative	Negative
Breast Tissue Culture	Negative	Negative

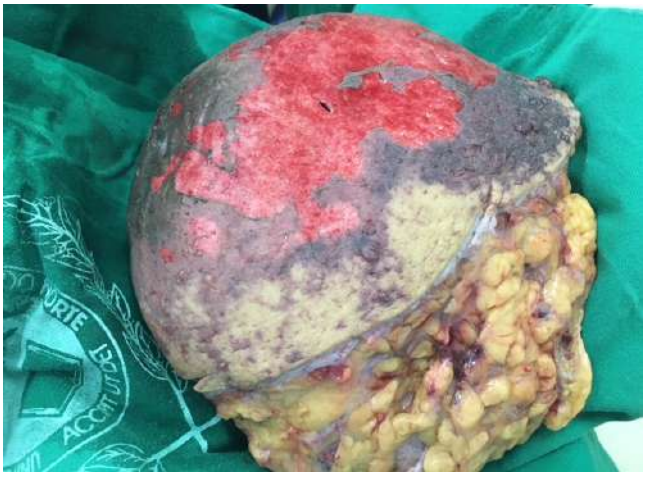

Figure 2. Wide surgical excision of necrotic tissue (right mastectomy).

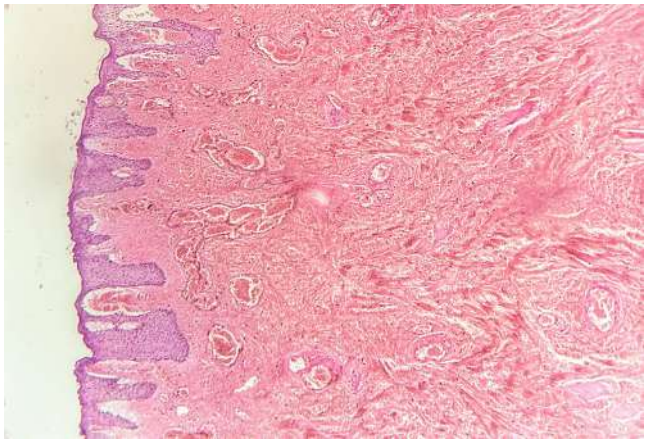

Figure 3. Histology showing extensive areas of vascular congestion and tissue hemorrhage (Haematoxylin and eosin stain — H&E, X40 magnification).

third of cases[5]. We describe a case of NF in the right breast of a healthy woman after a cesarean section with all negative cultures.

Classic manifestations of NF include soft-tissue edema, erythema, severe pain, tenderness, fever and skin bullae or necrosis[1]. The sonographic findings are fascia's irregularity, abnormal fluid collections along fascial planes, and diffuse thickening of the fascia[6].

Only a few cases of necrotizing fasciitis in the breast[3-5,7-15] have been reported in the literature; and due to the high mortality rate, early recognition and surgical debridement are of absolute importance. Emergency surgical debridement of the affected tissues is the primary management modality for NF. Surgical management is indicated especially for patients with intense pain and changes of skin color (such as edema and/or ecchymoses), or in signs of skin ischemia with blisters and bullae. It is also indicated when the individual presents altered mental status, hypotension and metabolic acidosis, as in the case described[2].

Although surgical treatment with mastectomy adopted in this case has been performed in other cases[4,7,9,11,13], there have been reports of successful treatment with conservative surgery[3,8,12,14,15] and even without surgery[10]. Lee et al.[10] reported a case of NF of the breast in a pregnant woman successfully treated using negative-pressure wound therapy.

Pharmacologic treatment for mixed aerobic and anaerobic infections of gynecologic organs should be based on Gram's staining, culture, and sensitivity tests. The Infectious Diseases Society of America (IDSA) publishes guidelines for the treatment of skin and soft-tissue infections. The current guidelines recommend vancomycin or linezolid in addition to one of the following therapies: piperacillin–tazobactam, carbapenem or ceftriaxone–metronidazole[1]. Some of these antibiotics were used in the case.

CONCLUSION

We present a rare case of primary NF of the breast with no history of tissue insult. The infection may be mistaken for cellulitis, puerperal mastitis or an abscess due to delayed cutaneous findings. Prompt diagnosis and rapid surgical intervention is crucial and can mean the difference between life and death in these critically ill patients. Despite this, NF still carries a high mortality rate.

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CASE REPORT
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ICE BURN IN PUERPERAL BREAST: CASE REPORT

Lesão térmica por gelo em mama de puérpera: relato de caso

Márden Pinheiro Teixeira Costa[1]*, Francisco Pimentel Cavalcante[1]

ABSTRACT

Burns are among the most severe injuries the human body can withstand, as they are life-threatening and therefore require prompt treatment with debridement and use of biological substitutes for a better prognosis. This case report concerns an 18-year-old patient on the 42nd day of puerperium who used ice packs on the right breast to alleviate breast engorgement and pain. After a prolonged period of use, it progressed to hyperemia and, subsequently, an extensive area of necrosis in the skin of the right breast, reaching the subcutaneous adipose tissue, compatible with a third-degree burn. Surgical debridement of the necrotic areas was performed, followed by the use of biological skin substitutes until complete healing of the local skin, not requiring grafting at first. Cryotherapy should be used with caution. Treatment with clinical support and fast surgical intervention can minimize the impact of burns.

KEYWORDS: Burn; breast; debridement; postpartum period; frostbite.

RESUMO

As queimaduras estão entre as mais graves lesões que o corpo humano pode suportar, visto que ameaçam a vida e requerem, portanto, um tratamento precoce com debridamento e uso de substitutos biológicos para melhora do prognóstico. O presente relato de caso diz respeito a uma paciente de 18 anos de idade no 42º dia de puerpério que realizou compressas com gelo na mama direita para melhora de ingurgitamento mamário e mastalgia. Após longo período de uso, evoluiu com hiperemia e, posteriormente, extensa área de necrose na pele da mama direita, atingindo o tecido adiposo subcutâneo, compatível com uma queimadura de terceiro grau. Foi realizado debridamento cirúrgico das áreas de necrose, seguido do emprego de substitutos biológicos da pele até a completa cicatrização da pele local, não necessitando de enxertia em um primeiro momento. Recomenda-se que a crioterapia deve ser utilizada com cautela. O tratamento com suporte clínico e a intervenção cirúrgica rápida podem minimizar o impacto das queimaduras.

PALAVRAS-CHAVE: Queimadura; mama; desbridamento; período pós-parto; congelamento das extremidades.

Study carried out at the Hospital Geral de Fortaleza – Fortaleza (CE), Brazil.
[1]Hospital Geral de Fortaleza – Fortaleza (CE), Brazil.
***Corresponding author:** mardenptc@gmail.com
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INTRODUCTION

Burns are among the most severe injuries the body can withstand – not only for the symptoms but the possibility of hypovolemic and septic shock, proportional to the extent and depth of the affected area, resulting in risk of life[1]. Therefore, burns require immediate treatment due to their urgency[2]. This event can cause prolonged periods of hospitalization, pain, edema, and deformity of the affected areas. The impact is not restricted to physical damage and can compromise psycho-emotional and relational aspects[3]. Prognosis improved dramatically in recent years, mainly thanks to the recognition of the importance of early debridement[4,5] and the progress in the use of biological skin substitutes[6].

Cryotherapy can cause burns. Widely adopted by health professionals, this treatment can cause skin damage if improperly done. In this study, the authors report a case of ice burn in one breast during the puerperium. This case is relevant not only for its rarity but also to emphasize the importance of correct instructions to prevent similar conditions from happening more often, in addition to guiding the conduct in these situations[7].

CASE REPORT

An 18-year-old patient on the 42nd day of puerperium visited the Mastology Department of Hospital Geral de Fortaleza (HGF) on July 6, 2017. She reported initial right breast pain and engorgement, which lead family members and healthcare professionals in her hometown to advise her to apply ice packs locally. After using the ice pack for more than three to four hours on the right breast, she noticed persistent hyperemia that progressed in a week to skin darkening in almost the entire right breast. She stopped breastfeeding and was instructed to apply local dressings with dermatological ointments, without improvement, being then referred to HGF.

Initial medical care identified an extensive area of total necrosis in the skin of the right breast, reaching the subcutaneous adipose tissue, with leakage of milk secretion due to the wound, compatible with a third-degree burn. The nipple-areola complex (NAC) was preserved, as an "island" in the middle of the necrotic tissue (Figure 1). No nodular area was found in the breasts and axillae. She was hospitalized and started antibiotic therapy/prophylaxis with ciprofloxacin and clindamycin, in addition to Cabergoline to suppress lactation.

On July 7, 2017, she underwent surgical debridement of the necrotic areas on the right breast, without complications (Figure 2), and with careful NAC preservation. She stayed in the hospital for three days with collagenase-based dressings and was discharged after evaluation by the Enterostomal Therapy Department. The patient applied Polyhexanide (PHMB) at home daily and changed dressings at the Enterostomal Therapy Outpatient Clinic with regenerative membrane/silicone mesh of low adherence weekly for five months.

The progress of the injury was satisfactory, with centripetal epithelialization over the months, not requiring skin grafting (Figure 3).

DISCUSSION

Approximately one million people suffer burns annually in Brazil. The main victims are children and low-income people. The public health system (*Sistema Único de Saúde* – SUS) registered more than 15 thousand cases of hospitalization due to burns in children aged 0 to 10 years between 2013 and 2014[8]. Burn is an injury caused by

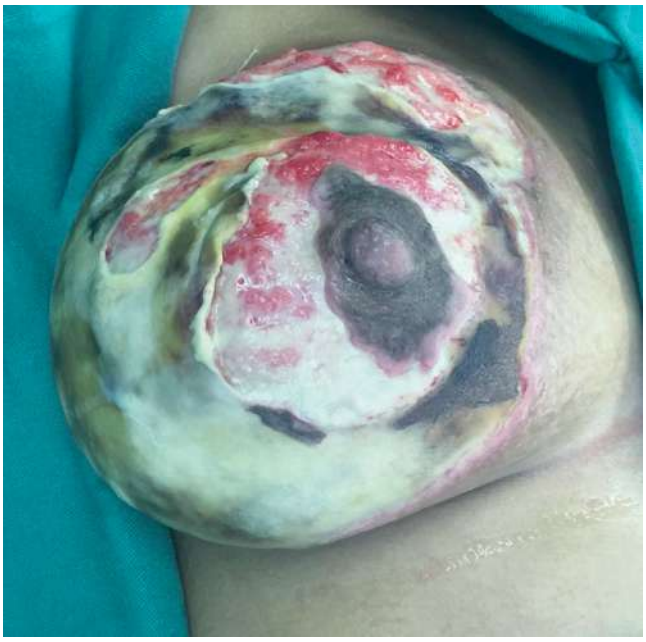

Figure 1. Initial aspect of the ice burn on the skin of the right breast.

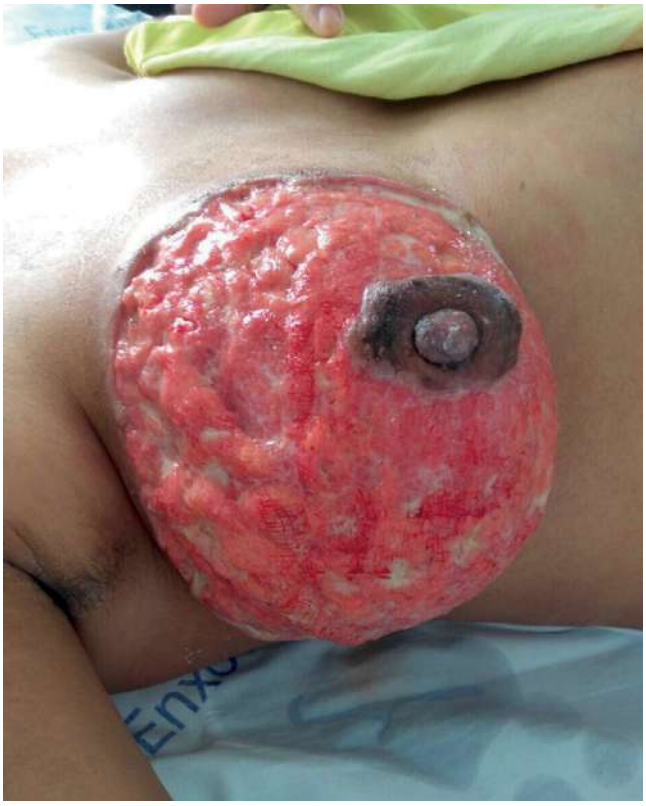

Figure 2. Aspect of the right breast after surgical debridement.

direct contact with a source of heat or cold, chemical products, electric current, radiation, or even some animals and plants (such as larvae, jellyfish, urtica), among others. For children, there is a risk of death if the burn reaches 10% of the body. In adults, the risk exists if the affected area exceeds 15%.

Children and young adults are known to be at higher risk of burn injuries. Severe burn injury, when not promptly and correctly treated, can cause deformities, mutilations, and gross cosmetic changes, which could have a noticeable impact on the future development of these individuals, compromising their biopsychosocial relationships and leading to psychiatric disorders. Therefore, early intervention improves quality of life and stimulates the formation of a strong identity, with lower impairment in the psychofunctional integrity of these patients[9]. Cryotherapy can cause burns, mainly in the extremities or periphery of the body, e.g., fingers, ears, and nose. Nevertheless, ice burns in central areas, such as the chest, are uncommon. Ice can cause vasoconstriction, reduce oxygen consumption and local metabolism, and form ice crystals in cells, with architectural change and cell death, affecting the skin and subcutaneous tissue in variable depth. Patients and health professionals use ice therapy after trauma to relieve pain, and for its anti-inflammatory effects. In spite of these benefits, the inappropriate use of ice, particularly in skins with reduced sensitivity — for instance, the skin of a puerperal woman, a breast biopsy site, or even a mastectomy flap — can lead to significant damage undetected by the patient during exposure. In the present case, the patient did not report significant symptoms during cryotherapy, noticing the hyperemia when the damage was already irreversible.

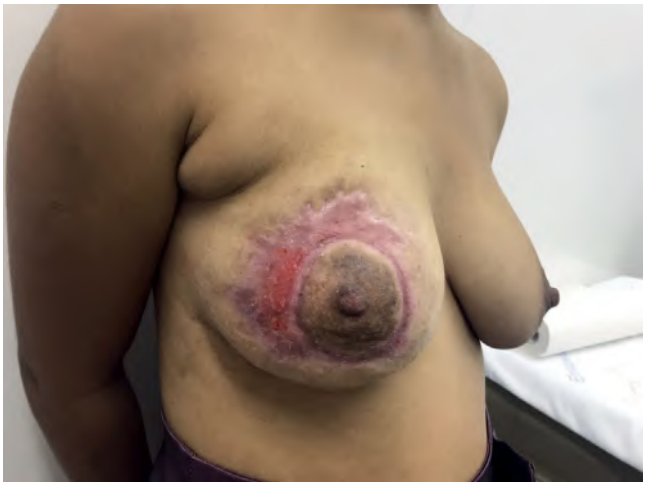

Figure 3. Aspect of the epithelialization after five months.

Burns can affect different skin layers, being didactically divided into degrees according to the depth. A first-degree burn reaches only the epidermis, while second-degree burns affect a deeper skin layer, usually with good clinical progress. A third-degree burn destroys the skin, reaching the epidermis, dermis, and potentially subcutaneous tissues, such as fat and muscle. Treatment consists of resection of the lesion with the removal of devitalized tissue, leaving an ulcerated wound, which can lead to a defective scar, fibrosis, retractions, and even movement changes, as happens in the limbs. In the case reported, despite the extensive third-degree burn, after adequate debridement and application of biological dressings, there was a progressive and gradual regeneration of the skin and satisfactory cosmetic result regarding breast volume and shape. Later, the patient will undergo a reduction mammaplasty to correct the asymmetry and minimize the scars.

CONCLUSION

Cases such as the one described contribute to guiding the prevention of thermal injuries in the breasts. Cryotherapy should be recommended with caution, especially in cases of reduced sensitivity. Proper patient instruction is crucial. Treatment with clinical support, fast surgical intervention, and care by the multidisciplinary team can minimize the impact of burns.

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REVIEW ARTICLE
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RADIOTHERAPY IN BREAST DUCTAL CARCINOMA *IN SITU*

Radioterapia em carcinoma ductal *in situ* de mama

Gustavo Nader Marta[1,2,3]*, Heloísa de Andrade Carvalho[1,3]

ABSTRACT

Breast ductal carcinoma *in situ* (DCIS) comprises a heterogeneous group of lesions with different forms of clinical and pathological presentation. Postoperative radiotherapy is usually performed in DCIS patients who underwent conservative breast surgery. The objective of the present study was to describe indications and clinical evidences of radiotherapy for breast DCIS patients.

KEYWORDS: Breast; ductal carcinoma in situ; radiotherapy.

RESUMO

O carcinoma ductal *in situ* (CDIS) de mama compreende um grupo heterogêneo de lesões com diferentes formas de apresentação clínica e patológica. A radioterapia pós-operatória é normalmente realizada nas pacientes com CDIS submetidas à cirurgia conservadora de mama. O presente estudo teve o objetivo de apresentar as indicações e as evidências para a utilização da radioterapia na abordagem do CDIS de mama.

PALAVRAS-CHAVE: Mama; carcinoma ductal in situ; radioterapia.

Study carried out at the Radiotherapy Service, Hospital Sírio-Libanês – São Paulo (SP), Brazil.
[1]Hospital Sírio-Libanês – São Paulo (SP), Brazil.
[2]Instituto do Câncer do Estado de São Paulo Octavio Frias de Oliveira – São Paulo (SP), Brazil.
[3]Faculdade de Medicina da Universidade de São Paulo – São Paulo (SP), Brazil.
***Corresponding author:** gustavo.marta@hc.fm.usp.br
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INTRODUCTION

Ductal carcinoma in situ (DCIS) of the breast comprises a heterogeneous group of lesions with different forms of clinical and pathological presentation. Traditionally, DCIS is classified according to its architectural pattern, which is usually encompassed in five main subdivisions: comedo, cribriform, micropapillary, papillary or solid[1]. It's a distinctive set of proliferative lesions with heterogeneous invasion potential. Therefore, identifying lesions with more aggressive potential is necessary to establish the most appropriate therapeutic proposal[1].

DCIS diagnosis has increased very markedly over the last years due to population-based mammography screening programmes[1]. When radical mastectomy was the method of choice to approach DCIS, cure rate was close to 98%, with low recurrence rate after surgical procedure[2].

With the advent of conservative treatment (quadrantectomy/lumpectomy followed by whole breast radiotherapy) for invasive breast carcinomas, this type of therapy started being used for DCIS (specially for small and unicentric tumors), though it's important to mention that there are only retrospective studies backing this kind of approach for DCIS. Therefore, there are no prospective or randomized clinical trials comparing conservative therapy and radical mastectomy for these patients[3,4].

Whole breast radiotherapy after conservative surgery reduces the risk of local recurrences (both *in situ* and invasive). Local control benefits are the most significant gains of this approach and the results are more significant when combined with radiotherapy, even though there are no direct gains regarding overall survival rates.

THE ROLE OF ADJUVANT WHOLE BREAST RADIOTHERAPY FOR DUCTAL CARCINOMA *IN SITU*: CLINICAL EVIDENCE

Randomized clinical trials

Four randomized clinical trials with over 4,000 patients showed local control benefit when adjuvant radiotherapy was added to the treatment of DCIS patients who underwent conservative surgery.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-17 involved 818 patients randomly divided into two groups: whole breast isolated or radiotherapy-associated surgery. The main result was local recurrence (invasive or intraductal). In a 12-year follow-up, radiotherapy reduced the cumulative local recurrence rate (16.0 *versus* 32.0%). Considering invasive and non-invasive recurrences, in both subgroups the gains were maintained though the invasive recurrence decrease was higher than non-invasive recurrence (16.8 *versus* 7.7% and 14.6 *versus* 8.0%, respectively). There was no impact over overall or cancer-specific survival rates[5]. An update of this study (with conjoint analysis of NSABP B-24 data) corroborates the benefits of adjuvant radiotherapy[6].

The European Organization for Research and Treatment of Cancer (EORTC 10853) assessed 1,010 DCIS patients (with ≤5-cm tumors) treated with conservative surgery. The patients randomly received whole breast radiotherapy or a clinical approach. After 4.3 years of trial, the group treated with radiotherapy showed lower invasive (4.8 *versus* 8.0%) and non-invasive (5.8 *versus* 8.8%) recurrence rates when compared to the non-adjuvant group[7]. In 15 years, there was a 48% decrease in the risk of local recurrence, with a longer recurrence-free interval, over the same period for the radiotherapy group (82 *versus* 69%). No difference was observed between cancer-specific and overall survival[8].

A cooperative study conducted by researchers from England, Australia and New Zeeland randomly submitted 1,701 patients to DCIS surgery with free margins to the following groups: isolated surgery, surgery with whole breast radiotherapy, surgery with tamoxifen treatment and surgery with both whole breast radiotherapy and tamoxifen treatment. After 53 months of follow-up, on average, radiotherapy was able to decrease the recurrence rate of *in situ* and ipsilateral invasive carcinoma. Hormone therapy did not reduce the occurrence of ipsilateral invasive tumors, although DCIS overall recurrence was shown to be lower[9]. After 12.7 years of study, it was once again confirmed that radiotherapy decreased the incidence of ipsilateral invasive tumors recurrence (*hazard ratio* 0.32; 95% confidence interval — 95%CI 0.19–0.56; p<0.0001) and *in situ* recurrence (*hazard ratio* 0.38; 95%CI 0.22–0.63; p<0.0001)[10].

An investigation by the Swedish Breast Cancer Group analyzed the role of whole breast radiotherapy after conservative surgery in 1,046 DCIS patients. After 5.2 years of study, the group that underwent radiotherapy showed less recurrences (44 *versus* 117 cases). No difference was observed between groups regarding contralateral breast cancer, distant metastasis and death rates[11]. A recent 20-year follow-up update of this study placed radiotherapy as related to a 37.5% reduction of ipsilateral recurrence risk. Once again, no impact on overall survival rates was observed[12].

The study 9.804 by the Radiation Therapy Oncology Group (RTOG) randomly submitted 636 DCIS patients (with unicentric tumor smaller than 2.5 cm and low or intermediate nuclear grade) to whole breast radiotherapy or to observation. The use of tamoxifen was optional (62% of the patients received it). With average follow-up of 7.17 years, local ipsilateral recurrence in the radiotherapy group was rare (2 *versus* 19 occurrences). In a seven-year period, local recurrence rate was 0.9% in the radiotherapy group and 6.7% in the observation group (*hazard ratio* 0.11; 95%CI 0.03–0.47; p<0.001)[13].

It is worth noting that studies NSABP B-17[6] and EORTC[8] pointed out the benefits of radiotherapy even for the subgroup of patients considered at low risk (free surgical margins, >2-cm tumors and low-grade lesion). Also importantly, even though there were no direct overall survival benefits, breast cancer mortality rate was higher among patients with ipsilateral breast invasive carcinoma recurrence.

Some of the aforementioned studies, however, have limitations mainly regarding pathological evaluation (measurement of the tumor size and definition of free margins), surgical specimen radiography, and postoperative mammography.

Table 1 sums up the characteristics and results of randomized clinical trials selected.

Meta-analysis

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published in 2010 a meta-analysis compiling data from clinical trials and showed an absolute risk reduction of 15.2% over ten years when whole breast radiotherapy was combined with conservative surgery. The benefits of radiotherapy were the same regardless of age, surgery type (quadrantectomy or lumpectomy), use of tamoxifen, diagnosis method (clinical or radiologic), surgical margin (free, narrow or unknown), nuclear grade, presence of comedonecrosis, architectural subtype or tumor size. Furthermore, the impact of radiotherapy on the outcome was similar in terms of *in situ* and invasive local recurrences: 6.5 versus 14.9% and 6.9 *versus* 15.4%, respectively. The analysis of the subgroup of patients rated as low-risk (≤2-cm tumor, grade 1 and free margins) showed that radiotherapy was able to reduce the absolute risk of local recurrence by 18% (12 *versus* 30%; p=0.002)[14].

Another meta-analysis carried out by the Cochrane Group confirmed the statistically significant benefits of radiotherapy in cases of ipsilateral local recurrence (*hazard ratio* 0.49; 95%CI 0.41–0.58; p<0.00001), ipsilateral invasive recurrence (*hazard ratio* 0.50; 95%CI 0.32–0.76; p=0.001), and ipsilateral *in situ* recurrence (*hazard ratio* 0.61; 95%CI 0.39–0.95; p=0.03). Analysis of all subgroups showed benefits of adopting radiotherapy, with no long-term toxicity associated to this treatment[15].

RADIATION BOOST AFTER WHOLE BREAST RADIOTHERAPY FOR DUCTAL CARCINOMA *IN SITU*

The role of booster doses in the treatment of breast invasive tumors has been stablished through randomized clinical trials[16].

Regarding DCIS, a retrospective multicenter study showed, in a 72-month follow-up, that women younger than 45 years had local recurrence rates after conservative breast treatment of 54, 28 and 16%, considering patients treated exclusively with surgery, with surgery combined with whole breast radiotherapy, and with surgery combined with whole breast radiation boost on surgical bed, respectively[17]. Corroborating those results, other

Table 1. Randomized clinical trials.

Study	Recruitment period	Duration (years)	Number of patients	Pathology central revision (%)	Negative margins (%)	RT doses	*Booster doses*
NSABP B-17	1985–1990	17.25	818	76	78	50Gy/25 fractions	10 Gy/5 fractions (9% of the patients)
EORTC 10853	1986–1996	15.8	1.010	85	83	50Gy/25 fractions	10 Gy/5 fractions (5% of the patients)
UK/ANZ DCIS	1990–1998	12.7	1.030	0	100	50Gy/25 fractions	-
SweDCIS	1987–1999	20	1.067	26	80	50 - 54Gy/25 -27 fractions	-
RTOG 9804	1998–2006	7.17	636	100	100	50 - 54Gy/25 -27 fractions or 42,5Gy/16 fractions	-

Study	Local recurrence (%)						Overall survival (%)	
	Total		Invasive		*In situ*			
	Without RT	With RT	Without RT	With RT	Without RT	With RT	Without RT	With RT
NSABP B-17	35.0	19,8	19,6	10,7	15,5	9,0	86,0	87,0
EORTC 10853	30.0	17,0	15,0	9,5	15,0	7,5	90,0	88,0
UK/ANZ DCIS	19.4	7,0	9,1	3,3	9,7	3,8	97,9	96,2
SweDCIS	20.0	32,0	-	-	-	-	77,7	73,0
RTOG 9804	6.7	0,9	-	-	-	-	95,1	91,7

RT: radiotherapy; NSABP: National Surgical Adjuvant Breast and Bowel Project; EORT: European Organization for Research and Treatment of Cancer; RTOG: Radiation Therapy Oncology Group.

retrospective studies reported low local recurrence rates when booster radiation doses were systematically used[18,19].

However, some studies reported no benefit related to the use of radiation boost in the treatment of DCIS patients[21].

This matter remains open, and currently two randomized clinical trials are ongoing with the goal of evaluating booster doses for DCIS patients.

WHOLE BREAST HYPOFRACTIONATED RADIOTHERAPY FOR DUCTAL CARCINOMA *IN SITU*

The hypofractionated radiotherapy, which has a fraction number smaller than the standard 25 to 30, is becoming popular after the publishing of two studies that evaluated the long-term evolution of patients submitted to this procedure[22,23]. Treatment schemes with 15 and 16 radiotherapy fractions have been assessed. No differences between local control, survival rate and toxicity were observed, and schemes were deemed equivalent to standard, if not better in terms of late toxicity. Most patients included in both studies were aged over 50 years and had low-risk invasive tumors in early stages. Regarding DCIS, however, the hypofractionated schemes were not randomly tested.

Despite that, the appeal for a shorter-term, more efficient treatment led several health centers to evaluate the effects of hypofractionated radiation on DCIS, and the outcomes were all gathered in a meta-analysis of observational studies published in 2015. Among the 13 studies analyzed, four (2,534 patients) compared the hypofractionated radiation to standard fractioning, but found no differences in local recurrence rate between the groups (*hazard ratio*: 0.78, 95%CI 0.58–1.03). The authors concluded that hypofractionated radiotherapy seems to be safe and efficient for DCIS patients and can be used as long as professionals keep in mind that the studies included in the meta-analysis carry a low level of evidence[24].

WHOLE BREAST ADJUVANT RADIOTHERAPY IN ELDERLY PATIENTS WITH DUCTAL CARCINOMA *IN SITU*

The benefits of radiotherapy for low-risk DCIS patients is a controversial question, especially in advanced ages. Also, women over 70 years old either are generally not included in clinical trials or represent a small portion of the studied population. According to a data collection in France, only 13.4% of the studied DCIS patients were aged 70 years or older[25].

The best available data about conservative breast cancer treatment with or without radiotherapy in elderly patients (above 70 years old) come basically from two randomized studies conducted with early-stage invasive tumor patients. The patients submitted to radiation had good results as to local control, but overall survival rates were not impacted[26,27].

Regarding DCIS, the EBCTCG[15] meta-analysis also showed good outcomes of adjuvant radiotherapy after conservative surgery. Results were proportionally better in patients aged 50 years or older, with absolute risk of ipsilateral recurrence after 10 years of 18,5 *versus* 29,1% for patients below the age of 50 , and of 10,8 *versus* 27,8% for the other age groups. It is worth noting that the cut-off age was 50 years old, and still the risks with or without adjuvant radiotherapy in this group were lower compared to patients under this age. There are no specific data addressing patients over 70 years old, however, the proportional reduction of occurrences in the group receiving radiation therapy increased with aging, for every decade added: 60 to 69 and 70 and above (p=0.02).

Even elderly DCIS patients benefit in terms of local control from radiotherapy after conservative surgery and, to the present moment, there is not a subgroup of patients that can be safely kept from radiation therapy. Age alone can not be a contraindication for the treatment. In the long run, the potential impact of local recurrence on elderly patients' quality of life and psychological state should not be underestimated.

However, at least for patients with lower life expectancy, whether by presence of comorbidities or advanced age, the extent of risk reduction should be evaluated, keeping in mind that at least nine patients must be submitted to radiation therapy as a means of preventing ipsilateral recurrence[15]; among the elderly, this number can range from 20 or 21 (70 to 80 years old) to 160 (80 years and older) patients[28].

The International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA)[29] recommend that, once survival rates do not change, the level of local control must be assessed considering individual risk, physiological age, life perspective, treatment tolerance, patient's preference and other potential matters such as daily visits to the radiotherapy service for adjuvant therapy.

ACCELERATED PARTIAL BREAST RADIATION FOR DUCTAL CARCINOMA *IN SITU*

Accelerated partial breast radiation (APBR) has been evaluated in several randomized clinical trials. When compared to whole breast radiotherapy, results are controversial when it comes to local control rates. Some studies report similar local recurrence rates, while others point out lower rates in the group of patients submitted to APBR. It's important to emphasize that the number of DCIS patients included in such studies is small, hence it's difficult to outline the true effect of APBR in this subgroup of patients[30].

The American Society for Radiation Oncology (ASTRO)[31] and the American Brachytherapy Society (ABS)[32] consider DCIS patients good candidates to APBI. On the other hand, the European

Society for Radiotherapy and Oncology (ESTRO) states that new studies are necessary to prove the efficiency of APBI for DCIS patients and they do not recommend this therapy as a routine procedure[33].

CONCLUSIONS

- Whole breast adjuvant radiotherapy is related to reduction of *in situ* and invasive recurrences in breast DCIS patients. Therefore, it should be adopted as a routine procedure;
- The action of booster radiation doses in the treatment of DCIS patients is not clear;
- Hypofractionated radiotherapy can strongly be regarded as a procedure for DCIS patients, following the same selection criteria used for invasive tumors;
- For elderly DCIS patients, the indication of radiotherapy must be based on the balance between treatment benefits and patients' life perspective;
- APBI for DCIS patients is a controversial matter despite some international guidelines supporting its use in clinical practice.

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REVIEW ARTICLE
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ENDOCRINE DISRUPTORS AND THEIR INFLUENCE IN THE ORIGIN OF BREAST NEOPLASM AND OTHER BREAST PATHOLOGIES

Disruptores endócrinos e o seu papel na gênese das neoplasias e de outras patologias das mamas

Mauri José Piazza[1]*, Almir Antônio Urbanetz[1], Cicero Urban[2]

ABSTRACT

A higher occurrence of early breast cancer in women has created the need to identify possible etiologic agents characterized as direct co-responsible. The motivation for this review is the relevance of detecting potential endocrine disruptors responsible for harmful effects on breast tissue and, consequently, its damage.

KEYWORDS: Breast; breast cancer; breast neoplasms.

RESUMO

Uma maior ocorrência no surgimento precoce das neoplasias das mamas em mulheres tem gerado a necessidade da descoberta dos possíveis agentes etiológicos caracterizados como corresponsáveis diretos. A relevância da detecção dos possíveis disruptores endócrinos responsáveis por exercer efeitos danosos nos tecidos mamários e, consequentemente, o seu comprometimento é a motivação da presente revisão.

PALAVRAS-CHAVE: Mama; câncer de mama; neoplasias da mama.

Study conducted at Universidade Federal do Paraná – Curitiba (PR), Brazil.
[1]Department of Obstetrics and Gynecology, Universidade Federal do Paraná – Curitiba (PR), Brazil.
[2]Universidade Positivo – Curitiba (PR), Brazil.
***Corresponding author:** mauripiazza@hotmail.com
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INTRODUCTION

In recent decades, a higher incidence of hormone-dependent neoplasms has been observed in body parts such as breasts, endometrium, ovaries, testicles, prostate, and thyroid. Despite the recent increase in implementation of methods for early diagnosis, numerous other possible etiologic factors — such as dietary habits and use of pharmaceutical or chemical drugs — may share the responsibility for the greater occurrence of these neoplasms.

This review proposes an analysis of possible deleterious actions of carcinogenic agents — known as endocrine disruptors (ED) — that could be involved in the onset of various pathologies and breast neoplasms, and possibly implicated in these areas in several animal species.

Among many agents considered to be ED, we have:

1. Bisphenols (Figure 1): constitute a wide range of substances. Their first synthetization was in 1891, but in 1936, evidence of estrogenic activity[1] was found in Bisphenol A (BPA). Their annual production continually expands due to large consumption and diverse use in products like toys, plastics, food packaging, and in epoxy resins. BPA can be ingested or act via transdermal or sublingual routes and undergoes fast liver metabolization[2-4]. Because it is lipophilic, it accumulates in fat tissues. Since 1950, it is possible to polymerize BPA to produce polycarbonate plastic, which is very flexible, lightweight, transparent, and resistant to heat and various chemicals. Five other bisphenols are in current use: bisphenol B (BPB), bisphenol F (BPF), bisphenol S (BPS), bisphenol AF (BPAF) and tetrabromobisphenol A (TBBPA);
2. Phthalates (Figure 2): phthalates and phthalate esters are also commonly used in the plastic and toys industries, in cosmetics, and in medical tubing manufacturing. Because of its broad dissemination in the world, this substance is also used by the food industry in products such as fruit juices, sports drinks, food supplements, and frozen food such as ice cream[5];
3. Atrazine (ATR) (Figure 3): atrazine (2-chloro-4-ethylamino-6-isopropylamino-s-triazine) is widely used as an herbicide to control weeds in crops of corn, soy, and sugar cane. It remains active for a long time, and, consequently, contaminates water tables and is responsible for abnormalities in many aquatic organisms, according to Solomon et al.[6];
4. Polychlorinated biphenyls and polybrominated biphenyl esters: this group of aromatic chemical substances has a

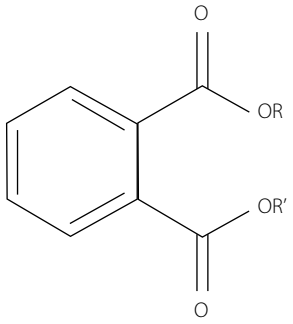
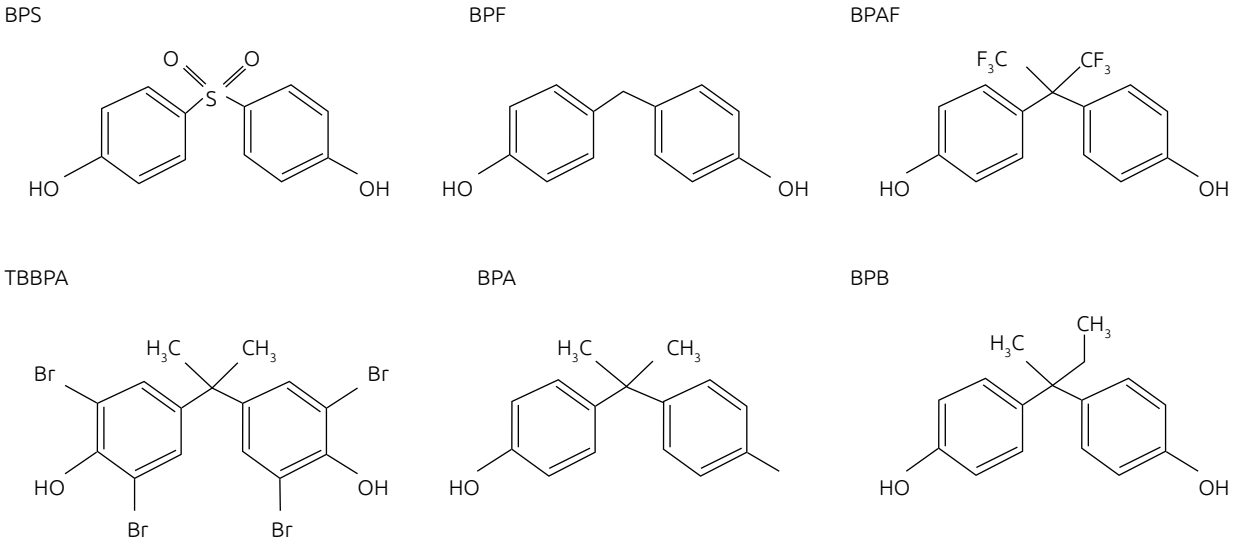


Figure 2. Structural formula of phthalates.



BPS: bisphenol S; BPF: bisphenol F; BPAF: bisphenol AF; TBBPA: tetrabromobisphenol A; BPA: bisphenol A; BPB: bisphenol B.

Figure 1. Structural formulas of bisphenols.

phenolic aromatic ring with chlorine or bromine radicals and is highly toxic. The synthetization of these products started in the late 1920's, but some of them were banned in 1979 for their toxicity. However, due to their multiplicity, others have been used in the plastic, rubber, adhesive, dye, and resin industries. Some of these products have thyroidogenic, estrogenic, or antiandrogenic activities[7,8]. Polybrominated diphenyl ethers (PBDE) used to be used as flame retardants in upholstered furniture, mattresses, and even in clothing production[9];

5. Dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyldichloroethane (DDD): DDT is an insecticide with long average life and lipophilic activity, which unfortunately has become a major environmental contaminant. The United States banned DDT in 1972, despite its benefits in reducing malaria and typhus[10,11]. DDE and DDD are metabolites of DDT, the latter being associated with the origin of endocrine diseases like diabetes mellitus type 2, and endometrial, pancreatic and breast cancers[12-14].
6. Diethylstilbestrol (Figure 4): powerful nonsteroidal estrogen synthesized in 1938 and formerly used in the United States for the treatment of threatened abortion and its possible complications[12]. Its initial dose was 5 mg/day, being progressively increased to 125 mg/day until the total dose of 3,650 to 4,000 mg.

However, in 1953, a study by Dieckman et al. proved its ineffectiveness for this indication[13]. In 1971, a work by Herbst et al. examined young women whose mothers had used this substance during their pregnancies and described a higher occurrence of vaginal adenosis-adenocarcinoma among them. In 1976, the same author reported other abnormalities in the female genital apparatus[14,15]. Also, Harris and Warring (2012) and Troisi (2014) found a higher incidence of genital abnormalities such as cryptorchidism in boys whose mothers had used the same substance. Daughters of these women also presented an anomaly described as T-shaped uterus and more occurrence of hormone-dependent tumors[16,17].

ONCOGENIC ACTIONS OF BREAST DISRUPTORS

Component of mammal reproductive system responsible for lactation, the mammary gland is particularly sensitive to ED as it involves systems of growth, differentiation, secretory activities and also of regression, all under the influence of hormones and numerous growth factors. As a result, the breast tissue is quite influenceable in very distinctive ways during three phases of life: puberty, pregnancy, and breastfeeding.

In the course of a pregnancy, when the breast buds receive a signal to form ducts and their extension to the underlying fat tissue, many ED can change the formation of mammary structures. Also, ED actions are deleterious to breasts in puberty since they grow exponentially by proliferating when a fast division of terminal mammary ducts and of the breast bud occurs.

Higher risk of breast neoplasms has been correlated with the early start of puberty and menarche, menopause at a late age, nulliparity, late first pregnancy, and obesity in pre-menopause.

There is a large number of chemical substances associated with the development and growth of breast tissue that pose a higher risk of breast neoplasms due to their actions.

The carcinogenicity of various substances

A study conducted with rodents in 1982 by the *United States National Toxicology Program* established that a BPA dose of 75 to 150 mg/kg weight/day is enough to exert carcinogenic activity. For its weak evidence, this study was questioned as to numerous factors, such as the non-inclusion and evaluation of these animals in their perinatal period[18]. In their studies — which included the periods of gestation and lactation with oral doses of 10 to 250 ug/kg weight/day —, Timms et al. (2005) and Moral et al. (2008) observed proliferative lesions in the mammary ductal epithelium and also prostatic squamous metaplasia in newborn

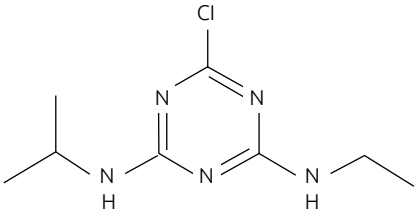


Figure 3. Structural formula of atrazine.

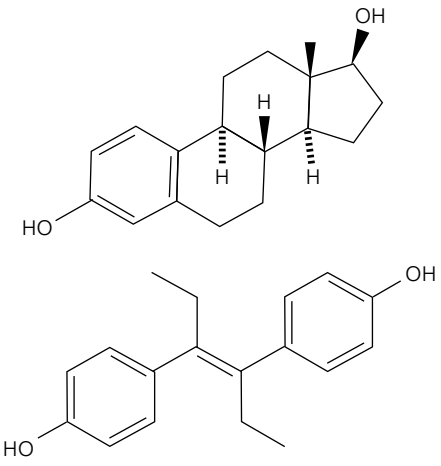


Figure 4. Structural formulas of estradiol and diethylstilbestrol.

rats, lesions susceptible to neoplasms[19,20]. Posterior studies by Jenkins et al. (2009) and Prins et al. (2011) showed that these agents generated an early condition for the appearance of breast and prostatic intraepithelial neoplasms in these animals[21,22].

However, these studies, which consisted in the exposure of animals to BPA in specific periods of their lives, had some deficiencies in design, such as the small sample, failure in time of use and/or additional treatments they underwent. These limitations prevented a definitive conclusion about their oncogenic potential.

Despite a large number of existing chemical substances with activities that mimic sex hormones, organochlorines are the main responsible for deleterious effects in various locations. Among them, we have 1,1,1-trichloro-2,2-bis (p- chlorophenyl)-ethane (DDT) and its isomer, p'-DDT, both of which have estrogenic properties; 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene with antiandrogenic action; 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), considered an antiestrogenic; and polychlorinated biphenyl (PCB) and its congeners, which can have estrogenic or antiestrogenic activities[23-26].

DIOXINS

There are more than 400 types of dioxins, but out of them, 30 are toxic to humans, TCDD being the most toxic. TCDD is a substance with large lipophilic capacity and a long average lifespan (7 to 11 years) that has been used as herbicide and pesticide. For its antiestrogenic capacity, TCDD reduces plasma levels of estradiol and alters breast development. Studies in humans conducted in Belgium by Den Hond et al. (2002) and in the Netherlands by Leijs et al. (2008) assessed children living in areas contaminated by dioxin who showed evident signs of delay in breast development[27,28].

Another historical incident occurred in Seveso, Italy (1976), when a large amount of TCDD was released in the environment.

Subsequent studies — which monitored all people contaminated in neighboring areas, dividing them according to degree of contamination — allowed the analysis of a possible higher incidence of neoplasms throughout the years.

According to Bertazzi et al. (1989 and 1997), the 10 and 15-year follow-up analyses of this population did not show an increase in the occurrence of neoplasms or higher mortality[29,30]. On the other hand, a 20-year follow-up analysis demonstrated discrete higher incidence of neoplasms in the population group that suffered greater contamination[31]. Warner et al. (2002) reassessed the same population assessed by Seveso for the *Women's Health Study* aiming to explore the possibility of higher incidence of breast neoplasms. Subjects exposed to the dioxin incident early in childhood and who had plasma level 10 times above the acceptable showed a twice higher incidence of breast neoplasms. This group was not yet between 40 and 55 years of age, stage of life in which this neoplasm is more common[32].

Another epidemiological study carried out by Revich et al. in the Chepayevsk region of Russia, where dioxin contamination also occurred, revealed a higher incidence of breast cancer among women living close to contamination area[33].

Also, in several studies with animals — rodents exposed to dioxin, for example — there was a larger number of alterations in breast development, such as high deficiency in the development of lobules and their size[34,35]. Other studies with rats exposed to dioxin in the prenatal period, such as those by Brown et al. and Desaulniers et al., showed more cases of adenocarcinomas in the breasts[36,37].

Dichlorodiphenyltrichloroethane, dichlorodiphenyldichloroethylene, and dichlorodiphenyldichloroethane

Studies in humans revealed that DDT and DDE can reduce the ability to breastfeed in women, according to previous works by Rogan et al. and Karmaus et al.[38,39]. References and analyses of the *National Toxicology Program* showed that DDE acts similarly to estrogens or antiandrogens. Thus, it can interfere with hormonal levels during lactation[11].

For years, there has been a huge concern about these substances known as ED, and many studies about them have been conducted. They can exist in the environment or be manufactured, and even trigger breast cancer. As most of these studies are considered case-control, results are disparate, and it is difficult to draw a statistically significant conclusion. Another obstacle is the possible association of existing substances or contaminants that could be acting in a nefarious and simultaneous way, which could make it hard to reach an accurate conclusion.

Before 1995, seven case-control studies were produced and directed to analyze the concentration of different organochlorine substances in tissues or serum.

Wasserman et al. (1976) conducted the first study, which examined the presence of DDT or PCB metabolites in fragments of breast tissue fixed in formalin, collected from nine patients with breast neoplasms and five women of a control group. Lipids in breast fragments with neoplasia had higher concentrations of PCB than those in breast tissue of women from the control group. However, the concentration of the bigger DDT metabolite — p,p'-DDE — was significantly higher in the control group[40].

The second and third studies, by Unger et al. (1984) and Mussalo-Rauhamaa et al. (1990), analyzed the presence of DDE or DDT metabolites in a series of fragments of breast tissues from patients with neoplasms (newly dead) and a normal control group. None of them had different concentrations, only an increased level of beta-hexachlorocyclohexane. These results did not allow conclusions, since the tissue fragments used came from deceased women[41,42].

The fourth study, by Falck et al. (1992), investigated the presence of seven organochlorine substances in breast tissue from

women with breast neoplasms and a control group. The tissue from women with cancer had high levels of DDE and PCB, but after classifying participants by age group and tobacco use, the values were not statistically significant[43].

A fifth study, by Dewailly et al. (1994), examined the presence of positive or negative receptors for estrogen in neoplastic breast tissues and found a greater presence of PCB or DDE in distinct groups, but the number of samples used for this study was small, the reason inaccurate conclusion[44].

In 1993, Wolff et al. (sixth study) observed a cohort of 14,290 patients living in the New York City area who had been subjected to a screening mammogram between 1985 and 1991. Among them, 58 were diagnosed with breast cancer. Their mean age was 51 years, and 80% of them were white-skinned women, with high serum levels of PCB and DDE[45].

In 1994, Kriener et al. conducted another important study (seventh) with a group of women from California monitored from 1964 to 1971. They selected 150 patients who developed breast cancer and 150 for the control group. Three racial groups were assessed: Asian, black, and white women with similar ages. When the racial groups were examined separately, white and black women had higher serum concentrations of DDE compared to the control group, while Asian women had lower levels. Multivariate control studies aimed at monitoring body mass index, age at menarche, pregnancies, and menopausal status were used to evaluate estimated risks. After PCB levels were checked, Asian and white women showed lower values when compared to their control groups. Through statistical analysis and based on odds ratio (OR), the conclusion of the study was that there is no association between serum concentrations of organochlorines and increased risk for breast cancer, and that serum levels differ according to geographical location[46].

In the study by Wolff et al., serum levels of DDE were 7.7 ng/mL, when compared with the control group. In Krieger et al., the levels were 35 ng/mL for white women, 43.4 ng/mL for black women, and 50.8 ng/mL for Asian women. Black and Asian women had higher serum concentrations as compared to white women[45,46].

Studies prior to 1995 did not draw any conclusions on the possible association of levels of DDT, its metabolites, and PCB with greater risk of breast cancer. However, other important studies have been produced since then, mostly case-controls, to analyze the relationship between DDT, its metabolites or PCB, and adipose tissue or serum levels of these patients.

The study by van't Veer et al. evaluated DDE levels in relation to breast neoplasms in tissue samples from patients living in five European countries. The group consisted of post-menopausal women and included 265 people with neoplasms and 341 controls. Using logistic regression and adjusting for age, sex, body mass index, alcohol consumption, and age at the end of first pregnancy, the researchers observed that DDE levels varied according to the country where the patients lived, but that levels below 1.9 μg/g pose no risk of neoplasm. These results allowed to conclude that the level of exposure to DDE does not increase the risk of breast cancer[47].

Two other studies, by Liljegren et al. in Sweden and Guttes et al. in Germany, analyzed the presence of DDE and PCB in adipose tissue of breasts with carcinoma. After multiple analyses, they concluded that there was no correlation between the concentration of these substances and breast carcinoma in humans[48,49].

In 1996, a study by Sutherland et al. researched several compounds (*Charleston Heart Study*) in a cohort of 405 white and black women and detected DDE serum levels of 32.0 ng/mL between 1974 and 1975, similar to the findings by Krieger et al.[46]. During the follow-up, done until 1994, 20 women developed breast carcinoma, and, in regression models and analysis of other variables, no evidence of a greater occurrence of breast neoplasm with the increased DDE concentrations was found[50].

Hunter et al., analyzed a cohort of 12 thousand female nurses in the Nurses Health Study, with follow-up since 1976, to evaluate DDE and PCB blood levels in 240 women with breast cancer and in an equal number of women in a control group. Mean value of DDE was 6.01 ng/mL (with 6.97 ng/mL in the control group), while PCB were 5.08 and 5.16 ng/mL. After several multivariate adjustments and comparisons, the findings showed no association between higher plasma levels of organochlorines and increased risk of breast cancer[51].

Outside the Europe-United States axis, Lopez-Carrillo et al. (1997) investigated a Mexican population where DDT was used more often, including for malaria control. The group consisted of 141 women with breast neoplasms and a control group of the same size. The results were similar, with DDE serum levels of 4.75 ng/mL (4.07 ng/mL in the control group), and no other statistically significant result[52].

A study carried out in Copenhagen by Hoyer et al. (Copenhagen City Heart Study) with a group of 7,712 women who had their sera stored, followed by another from the Danish Cancer Registry, identified 240 women with breast cancer and 477 for control. Eighteen different pesticides and their metabolites were identified, as well as 28 different types of PCB. Through statistical tests and logistic regression analyses, no association with DDT and its isomers or any other PCB congener was found. Among many compounds studied, only dieldrin could be listed as possibly associated with breast cancer, with OR of 1.96 and 2.05[53].

Subsequent studies have shown, in an inconsistent way, that the use of DDT and/or its metabolites could induce a higher incidence of breast cancer. A case-control study performed by Cohn et al. specifically demonstrated that a higher incidence of these neoplasms depends on the age of exposure to DDT and DDE. High serum levels of p,p'-DDT correlated with age,

especially for those born before 1931, showed an increase in incidence up to five times in women subjected to such exposure before the age of 14[54].

Boada et al. carried out another study in the Gran Canary Islands (Spain), which evaluated the exposure to multiple organochlorine pesticides in humans and their diverse influences. After analysis of multiple variables, serum levels of DDE, DDD, and aldrin — Hexachlorocyclopentadiene, an insecticide — were found to be very high in women with breast cancer, when compared to a group of healthy women[55].

White et al. studied a group of women for the project Long Island Breast Cancer Study, where an acute exposure to DDT occurred, as to the presence of estrogen and progesterone receptors in women exposed to it under the age of 20. They observed an increased risk of breast neoplasm, in relation to a control group that did not suffer such contamination[56].

In a large meta-analysis, Ingber et al. demonstrated widely conflicting data and a diversity of results as to the association of DDT and DDE levels with the occurrence of breast neoplasms. These studies have a broad variety of data, such as age, menopausal status, study designs, and variables considerations that make it difficult to reach conclusions on this possible association[57].

BISPHENOLS

BPA is similar to estradiol and joins the alpha estrogen receptor with weak activity, but it has a strong affinity to the gamma receiver and G protein, being able to induce the proliferation of breast epithelial carcinoma cells through stimulation of the alpha estrogen receptor[58-60]. Many *in-vitro* studies and other methodologies conducted with rodents have shown that BPA can change breast development during its growth as well as induce a greater risk of growing tumors. Studies by Markey et al., Munoz de Toro et al., and Acevedo et al. showed that exposure to BPA at low doses in fetal and perinatal periods can stimulate, during puberty, the onset of pre-neoplastic lesions of various hyperplasia degrees; and also, when administered in doses higher than 2.5 μg of BPA/kg, it induces ductal adenocarcinomas[61-64]. An incident in Michigan, United States, in 1973, led to food contamination by polybrominated biphenyl, impacting 3,653 individuals. Due to the possible risk of death, they were monitored until 1991. Henderson et al. analyzed the occurrence of breast cancer in this group and found that subjects with PBB concentrations beyond 2 ug of BPA/kg had higher risk of developing these neoplasms, which was the case for 20 women diagnosed with breast cancer[65].

PHTHALATES

Wolff et al. conducted a study with 1,200 pre-pubescent girls in 2014 and observed a delay in pubertal and pubic hair development in those presenting urinary levels of phthalates with high molecular weight. The substance was considered responsible for the delay due to its antiandrogenic properties. In the same study, breast development was also late in girls with high urinary concentrations of phthalates[66].

A study by Lopez-Carrillo et al. performed in northern Mexico examined the association between urinary concentrations of phthalates and breast cancer. Phthalates were detected in 82% of women, and the concentration of monoethyl phthalate (MEP) was higher in patients with breast cancer than in control patients. As a conclusion, this exposure would increase the risk of neoplasm in 2.5 times as related to the control group[67].

Studies with the use of dibutyl phthalate (DBP) demonstrated induction of reproductive toxicity in rodents due to the weak union to estrogen receptors. Such exposure in pregnant rodents would be enough to induce, via lactation, a hypoplastic development of mammary alveoli in animals that had received DBP[68].

ATRAZINE

Epidemiological studies have showed little to no association between exposure to atrazine (ATR) in agriculture and higher occurrence of breast cancer. In 1997, a study carried out in Kentucky, United States, showed that the contamination of surface waters by ATR in 1991 and 1992 significantly increased the occurrence of breast cancer in women exposed. Later, in 1993 and 1994, when, in addition to surface waters, waters of greater depth were also analyzed, this association was not observed[69,70].

Muir et al. observed a positive association between the use of ATR and a higher incidence of breast cancer after a population study conducted in Lincolnshire and Leicestershire counties, in England, from 1989 to 1991, when pesticides were applied in urban and rural regions[71].

All these studies have limitations and do not seem to suggest that the risk increases after exposure to ATR. Several studies with rodents showed that the impact of the early use of ATR can change the development of mammary glands and reduce their growth when pregnant rats and their offspring are exposed to the substance.

Although ATR is not classified as a directly carcinogenic substance, its chronic use can increase the incidence of mammary adenocarcinoma in Sprague-Dawley female rats and of mammary hyperplasia in male rats when administered in high doses[72].

DIETHYLSTILBESTROL

Diethylstilbestrol (DES), a nonsteroidal estrogen previously used for the treatment of threatened abortion doses varying from 5 to 125 mg/day was proven to induce different anomalies throughout the years. In 1971, Herbst et al. revealed that the substance was responsible for inducing the emergence of vaginal neoplasms, such as adenosis or clear-cell adenocarcinoma of the vagina in

young women whose mothers had used DES when pregnant[15]. Harris and Waring (2012), and Troisi (2013) assessed the role of DES in triggering other anomalies such as cryptorchidism in boys, uterine abnormalities known as T-shaped uterus, and hormone-dependent neoplasms[17,18].

Studies in animals have shown that DES can induce breast abnormalities such as increased growth when pregnant or nursing animals received high doses of the substance[73]. When exposure to DES occurred in the prenatal period, the risk of developing breast tumors increased due to a significant rise in proteins like EZH2 (enhancer of zeste homolog 2- induction of methylation of histone) or histone methyltransferase, which are linked to the origin of breast cancer[74].

PERFLUOROOCTANOIC ACID

A surfactant substance chemically used as grease and water cleaner, insect repellent, or firefighting foam. It is also used in dental products or food packaging, and its average lifespan is 16 to 22 days in rats and 2 to 4 years in humans. When combined with estradiol, the perfluorooctanoic acid (PFOA) has estrogenic and antiestrogenic properties *in vitro*[75].

Due to these properties, PFOA was correlated with delayed pubertal development and increased risk of breast cancer growth[76].

A study from the Breast Cancer and Environment Research Program found a direct connection between PFOA serum levels and breastfeeding received by young girls from 6 to 8 years of age. A highly significant relationship between water sources was also found in areas of the north of Kentucky and previous lactation periods, which could promote delay in breast development during the pubertal stage[73].

Also, numerous studies with animals showed a direct relation between PFOA levels and changes in breasts development and function. Exposure to PFOA during pregnancy may delay the epithelial development of mammary glands and even increase the mortality of newborns. These breast changes can increase mammary hyperplasia risk with elevation in stroma density. These conditional factors can result in higher risk of breast cancer[77].

ENDOGENOUS AND EXOGENOUS STEROID HORMONES

The use of steroid hormones — either as hormone replacement therapy or contraceptive pills — has always merited continuous observation and analysis as to their possible deleterious effects. Ever since these numerous exogenous therapies started being administered, different tissues have shown varying degrees of responses, as they suffer great variability due to the cyclic alternation provoked by the endogenous production of various hormones. The possible time of action varies widely and depends on many acting factors such as dose, growth factors involved, and type of hormone.

The various hormone actions in the breasts differ from those in the uterus and endometrium. Endogenous estrogens cause cell proliferation in the mammary gland, and under the action of progesterone in the second phase of the cycle, maturation effects and structural changes in the glands occur.

Different studies have analyzed the use of hormone replacement therapy. The Nurse Health Study showed that the relative risk of breast cancer is 1.3 for those who use only estrogen and 1.4 for those who use estrogen combined with progestogens[78].

In 2002, the Women Health Initiative (WHI) analyzed the risks posed by hormone therapy during menopause in a large random group consisting of 16,608 patients. Among them, 290 had breast cancer. After monitoring this group for 5.2 years, the relative risk of developing this type of neoplasm was found to be greater among those under estroprogestative therapy than those who only made use of estrogen therapy[79].

Another important study carried out from 1996 to 2001 was the Breast Cancer and hormone-replacement therapy in the Million women Study, which monitored 1,084,110 women. Out of this group, 9,364 were diagnosed with breast cancer, and 637 died from the disease after a follow-up of 2.6 and 4.1 years. The relative risk of developing this disease was 1.66 higher among users of hormone therapy. Also, the risk was even greater for women who made use of estrogen-progestogen combinations. The results also varied slightly depending on the doses of estrogen-progestogen or on use pattern, that is, continuous or sequential[80].

Regarding the risk of higher incidence of breast cancer among pill users, two studies, conducted in 1991 and 1996, analyzed epidemiological data from 50 thousand users and 100 thousand women from a control group and reported a slight increase in relative risk of 1.2 to 1.5 in the group of users. However, there was no increased risk for women who used the pill for more than ten years[81,82].

A recent study by Manson et al. examined the relationship between menopausal hormone therapy and placebo for a follow-up period of 5 to 7 years, and mortality risk up to 18 years (WH, randomized trials), monitored in 40 centers. The study counted with 27,347 women with mean age of 63.4 years, of whom 80.6% were white-skinned. There were 7,489 deaths. In one group, 8,506 women received conjugated estrogens (0.625 mg) and medroxyprogesterone acetate (10 mg) for 5.6 years *versus* 8,102 receiving placebo; in another trial, 5,310 women received only conjugated estrogens while 5,429 received placebo in a follow-up of 7.2 years. All-cause mortality was 27.1% in the hormone therapy group and 27.6% in the placebo group, while total mortality by cancer was 8.2% in the hormone therapy group and 8.5% in the placebo group. The study concluded that, among post-menopausal women, hormone therapy associated with conjugated estrogens and medroxyprogesterone, followed up for 5.6 years, or the use of

only conjugated estrogens for 7.2 years does not indicate higher risk of all-cause mortality, cardiovascular diseases, or even cancer mortality in up to 18 years of monitoring[83].

FINAL ANALYSIS

This wide range of existing chemicals — used as pesticides, and in the plastic, resin, dye, and pigment industries, among others — always deserve relevant observations, since they constitute examples of environmental contaminants and can be harmful to health.

These numerous substances seem to be responsible and act as co-authors and facilitators in the development of many diseases, breast carcinoma included.

In conclusion, it should be noted:

- The incidence of breast cancer, as well as other female genital neoplasms, has been increasing, and ED and environmental factors are suspected to have contributed to this scenario;
- There are critical periods in the development of breasts, when their susceptibility to endocrine actions is greater;
- For several rodents, there are crucial periods affecting breast development, rendering them prone to mammary neoplasms;
- Dioxins are chemical disruptors that delay pubertal development of breasts, according to evaluations in girls and rodents;
- Epidemiological studies indicate the importance of observing the effects of disruptors in women with higher sensitivity to breast cancer;
- There is a need for further studies that could test various combinations of ED based on their chemical structure and the evaluation of several lines of pre-cancerous tissue, in order to determine possible mechanisms of action related to the origin of breast cancer.

In 2015, the International Federation of Gynecology and Obstetrics (FIGO)[84] proposed various and important recommendations:

- Exposure to toxic chemicals has worldwide reach and is harmful to human reproduction and associated with various diseases;
- Preventing exposure to these substances should be a priority for all;
- Such toxic chemicals cross all country borders through food, water, wind, and different businesses and, thus, they act globally;
- Serious measures should be taken to avoid that the manufacturing of these substances leads to their constant release into the environment, rendering them dangerous to the health of a vulnerable population.

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REVIEW ARTICLE
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PROGNOSTIC IMPACT OF MICRO-RNA EXPRESSION IN BREAST CANCER: SYSTEMATIC REVIEW

Impacto prognóstico da expressão de micrornas no câncer de mama: revisão sistemática

Bárbara Adaildes dos Santos Soares[1], Karlla Greick Batista Dias Penna[1], Vera Aparecida Saddi[1]*

ABSTRACT

Breast cancer is an important health problem worldwide and the identification of new prognostic markers is important in establishing the best treatment for each patient. MicroRNAs (miRNAs) are non-coding RNAs that regulate gene expression and that can be useful biomarkers for prognosis in breast cancer. The objective of this systematic review was to investigate tumor miRNA expression potentially associated with the prognostic factors of breast carcinomas. The search was done in the PubMed database; 1457 articles were initially found and 20 studies were included in the review. MiRNA-21 and miRNA-200b were the most commonly investigated in breast cancer prognosis. Lymph node metastasis was associated with the hyperexpression of miRNA-211, miRNA-301a and miRNA-370 and also associated with the hypoexpression of miRNA-124, miRNA-127, miRNA-129-5p, miRNA199-5p, miRNA-206, miRNA-218 and miRNA-339-5p. Distant metastasis was associated with miRNA-204 hypoexpression. Tumor size was associated with hyperexpression of miRNA-21 and miRNA-301a and also to the hypoexpression of miRNA-29b and miRNA129-5p. Lower survival rates were associated with the hyperexpression of miRNA-21, miRNA-301a and microRNA-711, and hypoexpression of miRNA-15a, miRNA-29b, miRNA-124, miRNA-129-5p, miRNA 199b -5p, miRNA-200b, miRNA-204, miRNA-206 and miRNA-218. On the other hand, higher survival rates were associated with the hyperexpression of miRNA-339-5p and miRNA-127 and also to the hypoexpression of miRNA-210. The results of this review emphasize the need to validate these findings in additional studies.

KEYWORDS: microRNA; breast cancer; prognosis.

RESUMO

O câncer de mama é um importante problema de saúde em todo o mundo e a identificação de novos marcadores prognósticos é necessária para estabelecer o melhor tratamento para cada paciente. MicroRNAs (miRNAs) são RNAs não codificadores reguladores da expressão gênica que têm sido evidenciados como biomarcadores úteis no prognóstico do câncer de mama. O objetivo desta revisão sistemática foi verificar o papel da expressão de miRNAs tumorais associados aos fatores prognósticos dos carcinomas de mama. A busca de estudos foi feita no banco de dados PubMed; 1.457 artigos foram inicialmente encontrados e 20 estudos foram incluídos na revisão. MiRNA-21 e miRNA-200b foram os mais comumente investigados em relação ao prognóstico do câncer de mama. A presença de metástase linfonodal foi significativamente associada à hiperexpressão de miRNA-211, miRNA-301a e miRNA-370 e também associada à hipoexpressão de miRNA-124, miRNA-127, miRNA-129-5p, miRNA199-5p, miRNA-206, miRNA-218 e miRNA-339-5p. Metástase a distância foi associada à hipoexpressão de miRNA-204. O tamanho do tumor foi associado à hiperexpressão de miRNA-21 e miRNA-301a e também à hipoexpressão de miRNA-29b e miRNA129-5p. Em relação à sobrevida global, menores taxas de sobrevida foram associadas à hiperexpressão de miRNA-21, miRNA-301a e microRNA-711 e à hipoexpressão de miRNA-15a, miRNA-29b, miRNA-124, miRNA-129-5p, miRNA 199b-5p, miRNA-200b, miRNA-204, miRNA-206 e miRNA-218. Por outro lado, maiores taxas de sobrevida foram associadas à hiperexpressão de miRNA-339-5p e miRNA-127 e também à hipoexpressão de miRNA-210. Os resultados desta revisão enfatizam a necessidade de validar esses achados em estudos adicionais.

PALAVRAS-CHAVE: microRNA, câncer de mama, prognóstico.

[1]Pontifícia Universidade Católica de Goiás – Goiânia (GO), Brazil.
***Corresponding author:** verasaddi@gmail.com
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INTRODUCTION

Breast cancer is one of the most frequent neoplasms in women and represents a major public health problem in the world due to its high incidence and mortality. Each year, more than 1.67 million women are diagnosed with this disease and about 522,000 still die from it, despite improvements in diagnosis and treatment[1]. In Brazil, 59,700 new cases of breast cancer are estimated for 2018, corresponding to a predicted risk of 56.33 cases per 100,000 women[2].

Cancer staging is a process used to determine the extent of disease in the body and the location of the tumor. It assists the clinician in the choice of treatment and in determining the patient's prognosis. According to the 8th edition of the American Joint Committee on Cancer (AJCC), the main aspects used in staging and determining prognosis in breast cancer include: tumor size or extent, presence of lymph node metastasis, presence of distant metastasis, estrogen and progesterone receptor expression, epidermal growth factor receptor (HER-2) overexpression, tumor grade, and histologic type[3].

Despite advances in the diagnosis and treatment of breast cancer, the molecular heterogeneity of this disease still poses a great challenge. It is, therefore, necessary to identify new biomarkers for it, in order to better predict the clinical outcomes, as well as to establish the most appropriate treatment for each patient. Recent researches have explored the possibility of using microRNAs (miRNAs) as diagnostic and/or prognostic biomarkers, since these molecules are implicated in the progression of breast cancer[4-6].

The miRNAs are defined as small, non-coding RNA sequences of approximately 22 nucleotides in length. They originate from genes that are transcribed by RNA polymerase II. During the miRNA transcription step, clamp or hairpin structures, named pri-miRNAs (primary transcript RNA), are generated by RNA polymerase II activity and, less frequently, by RNA polymerase III. Still within the nucleus, pri-miRNAs, by action of ribonuclease III, DROSHA and the DGCR8/Pasha cofactor, generate pre-miRNAs (miRNA precursor). The pre-miRNAs are then transported from the nucleus to the cytoplasm by the aid of Protein Exportin 5. The pre-miRNAs are subsequently processed by a second ribonuclease III, called Dicer, releasing mature miRNAs, which in turn are incorporated in the miRNA-induced silencing complex, which may target messenger RNA (mRNA) encoding a specific protein. Mature miRNAs regulate the expression of protein coding genes at the post-transcriptional level. Regulation is partial or complete, by pairing of mature miRNA to the 3' untranslated region (UTR) of the correlated messenger RNA (mRNA), inducing translation inhibition or degradation of the target messenger RNA (Figure 1)[7-9].

The miRNAs are involved in several physiological processes such as proliferation, differentiation, apoptosis and resistance to stress, but, when deregulated they can influence pathological processes, such as tumorigenesis[10,11]. Studies indicate that miRNAs are involved in the initiation and progression of human cancers because of their ability to regulate the actions of many oncogenes and tumor suppressor genes. Deregulation of miRNA expression is described in several types of cancer, including breast cancer[10,12,13]. The miRNAs can be studied in tumor tissues and biological fluids, such as serum or plasma. Differences in the expression of certain miRNAs in breast carcinoma tissues compared to normal tissues have been described in several studies and suggest that miRNAs may be promising biomarkers, useful for early detection and prognosis of breast cancer[4-6,14].

The study of the expression of miRNAs in breast cancer constitutes an area of growing research and of great relevance in the current scientific scenario. However, in the scientific literature, recent systematic reviews that have evaluated the association between the expression of tumor miRNAs and the prognostic aspects of breast cancer are scarce. In addition, the types of tumors evaluated, the miRNA expression quantification method, and the types of biological samples evaluated vary considerably, producing disconnected and even conflicting results

Some studies available in the literature have evaluated the expression of miRNAs only in triple negative breast tumors, others have evaluated the expression of circulating miRNAs, in serum or plasma, while others have investigated the expression

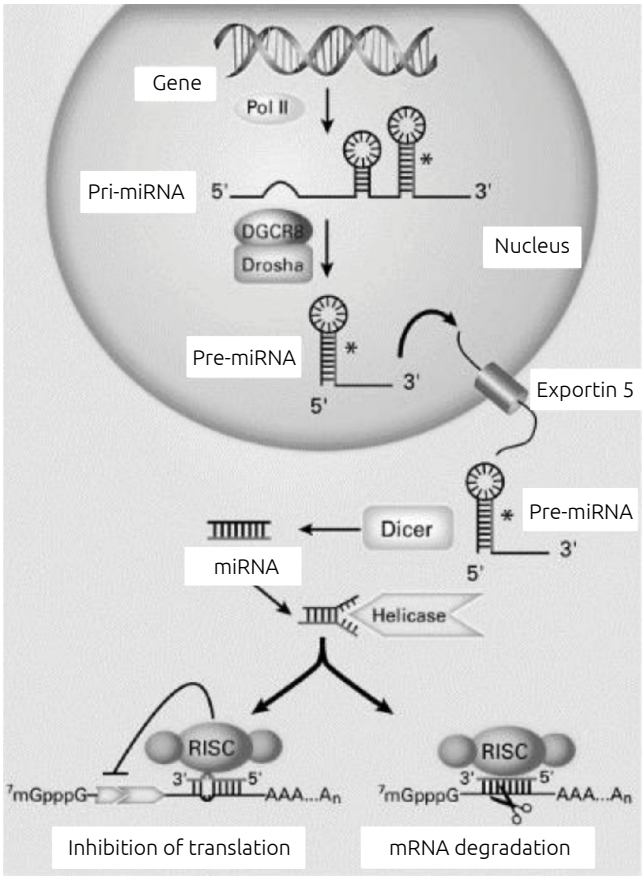

Figure 1. Biogenesis of miRNAs. Adapted from Iorio and Croce[9].

of miRNAs in association with specific clinical aspects, such as the presence of lymph node metastasis or disease recurrence, but there are few studies investigating the overall survival of patients as a function of miRNA expression. This study aimed to review the specific literature on the subject, with emphasis on the studies that evaluated the expression of miRNAs associated with the main prognostic factors in breast carcinomas, especially highlighting the impact of these biomarkers on patient survival.

METHOD

For the preparation of this study, a bibliographic review was performed in the PubMed database to identify relevant studies. Relevance criteria for the classification of studies included:

- studies published from 2002 to 2017;
- primary and descriptive studies;
- studies published in English;
- studies that evaluated the expression of miRNAs as a prognostic fator in breast cancer.

The search strategy adopted the following descriptors (microRNA OR miRNA OR miR) AND (breast cancer) AND (prognosis OR prognostic OR survival).

Relevance criteria for the study design included:

- studies that evaluated the prognosis of breast cancer through survival and/or the disease free interval;
- studies that evaluated miRNA expression through quantitative real-time polymerase chain reaction (RT-qPCR);
- studies that evaluated the expression of miRNAs in relation to tumor size, lymph node involvement by metastasis, distant metastasis, and triple and non-triple negative phenotype;
- studies that evaluated miRNA expression in freshly harvested or formalin-fixed tumor and included in paraffin specimens.

As exclusion criteria, publications that belonged to the category of case reports, literature reviews and meta-analyzes were not included. Two researchers reviewed the titles and abstracts of articles identified in the initial survey to determine the relevance of these publications.

The following data were extracted from the studies: first author, year of publication, number of participants, sample types, case origin, miRNAs studied, methods of miRNA expression evaluation and main results. The data were qualitatively reviewed and summarized in tables.

RESULT

Study selection

A total of 1,457 studies were initially identified through the electronic data search. After reviewing the titles and abstracts of these articles, 74 of them were selected, evaluating the expression of miRNAs in association with the prognosis of breast cancer. Then, careful reading of the full texts of these articles resulted in the exclusion of 54 of them. In total, 20 articles were eligible for systematic review. A flowchart of the study selection process is shown in Figure 2.

Characteristics of included studies

A total of 2,654 breast cancer patients were evaluated in the 20 included studies. The number of patients analyzed ranged from 30 to 344 per study. The researches considered were developed in countries such as Italy, South Korea, Iran, China and Japan — the last two were the ones with the most publications on the subject. The studies reported the prognostic values of 16 different miRNAs; the most studied were miRNA-21 and miRNA-200b: the first was investigated in four surveys, while the second, in two. The other selected studies investigated only a single miRNA. The selected studies used the quantitative real-time polymerase chain reaction (RT-qPCR) to evaluate the expression of miRNAs with TaqMan and SYBR Green quantification methodologies: TaqMan, used in 13 studies, was the most used one. SYBR Green was used in 7. The characteristics of the surveys included in the systematic review are shown in Table 1.

Studies evaluating the prognosis of breast cancer through survival and disease-free intervals have shown that miRNA hypoexpression was more associated with poorer prognosis than hyperexpression of miRNA. Regarding clinical-pathological characteristics, most of the studies showed that miRNA hypoexpression was more associated with lymph node metastasis than with miRNA hyperexpression. Table 2 shows the prognostic aspects related to the expression of miRNAs.

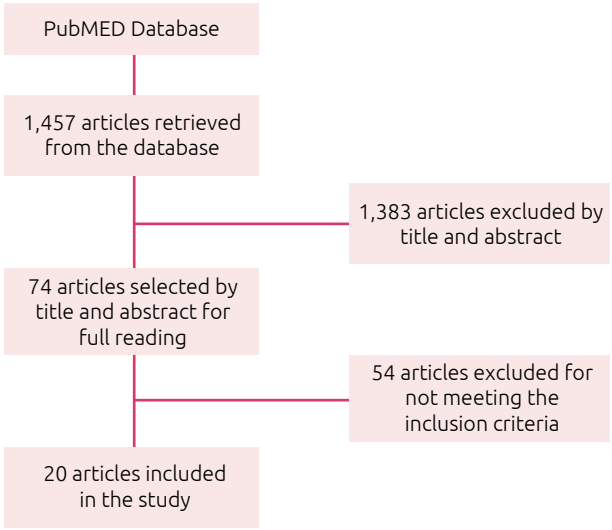

Figure 2. Flowchart of the study selection process.

Table 1. Characteristics of the studies included in the systematic review.

Author/year	miRNAs studied	Cases (n)	Origin of the cases	Quantification method	Results	Reference
Yan et al., 2008[14]	miRNA-21	Breast Ca (n=113) and normal tissue (n=40)	China	RT-qPCR TaqMan	Hyperexpression was associated with the worst prognosis.	14
Qian et al., 2009[10]	miRNA-21	Breast Ca (n=344)	Italy	RT-qPCR TaqMan	Hyperexpression was associated with lower disease-free survival in patients in the early stages.	10
Wu et al., 2010[19]	miRNA-339-5p	Breast Ca (n=90) and normal tissue (n=26)	China	RT-qPCR SYBR Green	Hypoexpression was associated with increased lymph node metastasis.	19
Lee et al., 2011[22]	miRNA-21	Breast Ca (n=109)	South Korea	RT-qPCR Taqman	Hyperexpression was associated with the largest tumor size and the lowest disease-free survival.	22
Toyama et al., 2012[24]	miRNA-210	Breast Ca (n=161)	Japan	RT-qPCR TaqMan	Hypoexpression was associated with better overall survival and better disease-free survival.	24
Li et al., 2013[18]	miRNA-206	Breast Ca (n=128)	China	RT-qPCR Taqman	Hypoexpression was associated with worse prognosis and distant metastasis.	18
Li et al., 2014[20]	miRNA-204	Breast Ca (n=129)	China	RT-qPCR Taqman	Hypoexpression was associated with lower overall survival, lower disease-free survival, and increased metastasis.	20
Dong et al., 2014[23]	miRNA-21	triple negative (n=72) and non-triple negative (n=14) Breast Ca	China	RT-qPCR SYBR Green	Hyperexpression was associated with worse prognosis and triple negative tumors.	23
Wang et al., 2014[16]	miRNA-127	Breast Ca (n=100)	China	RT-qPCR Taqman	Hypoexpression associated with lower overall survival.	16
Yu et al., 2014[11]	miRNA-301a	Triple negative Breast Ca (n=118)	China	RT-qPCR TaqMan	Hyperexpression was associated with lower overall survival, larger tumor size and lymph node metastasis.	11
Ye et al., 2014[21]	miRNA-200b	Breast Ca (n=40)	China	RT-qPCR SYBR Green	Hypoexpression was associated with a worse prognosis.	21
Shinden et al., 2015[26]	miRNA-15a	Breast Ca (n=230)	Japan	RT-qPCR TaqMan	Hypoexpression was associated with lower disease-free survival and lower overall survival.	26
Sim et al., 2015[15]	miRNA-370	Breast Ca (n=60)	South Korea	RT-qPCR SYBR Green	Hyperexpression was associated with lymph node metastasis and reduced disease-free survival.	15
Shinden et al., 2015[12]	miRNA-29b	Breast Ca (n=94)	Japan	RT-qPCR TaqMan	Hypoexpression was associated with lower overall survival and lower disease-free survival.	12
Dong et al., 2015[13]	miRNA-124	Breast Ca and normal tissue (n=133)	China	RT-qPCR SYBR Green	Hypoexpression was associated with lower overall survival, lymph node metastasis and low histopathological differentiation.	13
Yu et al., 2015[17]	miRNA-129-5p	Breast Ca and normal tissue (n=30)	China	RT-qPCR TaqMan	Hypoexpression was associated with lower survival.	17
Yao et al., 2015[25]	miRNA-200b	Breast Ca and normal tissue (n=278)	China	RT-qPCR SYBR Green	Hypoexpression was associated with lower survival.	25
Fang et al., 2016[4]	miRNA-199b-5p	Breast Ca and normal tissue (n=131)	China	RT-qPCR Taqman	Hypoexpression was associated with lymph node metastasis and decreased overall survival.	4
Hu et al., 2016[5]	miRNA-711	Breast Ca (n=161)	China	RT-qPCR TaqMan	Hyperexpression was associated with lower overall survival and lower disease-free survival.	5
Ahmadinejad et al., 2017[6]	miRNA-218	Breast Ca and normal tissue (n=33)	Iran	RT-qPCR SYBR Green	Hypoexpression was associated with lymph node metastasis, high grade and worse prognosis.	6

Breast Ca: breast cancer; RT-qPCR: quantitative real-time polymerase chain reaction.

microRNAs and the prognostic of breast cancer

miRNAs associated with the presence of lymph node metastasis

Three studies demonstrated hyperexpression of miRNA-21[14], miRNA-301a[11] and miRNA-370[15] associated with the presence of lymph node metastasis. On the other hand, seven of them demonstrated hypoexpression of miRNA-124[13], miRNA-127[16], miRNA-129-5p[17], miRNA-199b-5p[4], microRNA-206[18], miRNA-218[6] and miRNA-339-5p[19] associated with the presence of lymph node metastasis (Table 2).

miRNAs associated with the presence of distant metastasis

The hypoexpression of miRNA-204[20] and miRNA-200b[21] was associated with the presence of distant metastasis in two studies. No other study showed associations between hyperexpression of miRNAs and the presence of distant metastasis (Table 2).

miRNAs associated with tumor size

Hyperexpression of miRNA-21[22,23] and miRNA-301a[11] associated with tumor size was reported in three studies. The hypoexpression of miRNA-29b[12] and miRNA-129-5p[17] associated with tumor size was reported in two studies (Table 2).

miRNAs associated with triple negative phenotype

The triple negative phenotype is characterized by the absence of expression of estrogen, progesterone and HER-2 receptors in breast cancer. The hyperexpression of miRNA-210[24] and miRNA-301a[11] was associated with the triple negative phenotype in two studies, and miRNA-21[23] hypoexpression was associated with triple negative phenotype in a single study (Table 2).

miRNAs associated with the HER-2 positive phenotype

Hyperexpression of miRNA-21[22] was associated with HER-2 positive phenotype in one study, and miRNA-200b[25] hypoexpression was also associated with HER-2 positive phenotype in one study (Table 2).

miRNAs associated with overall survival

The hyperexpression of miRNA-21[10], miRNA-301a[11] and miRNA-711[5] was associated with poorer prognosis (lower overall survival) in six studies, while miRNA-127[16] and miRNA-339-5p[19] hyperexpression were associated with better prognosis (greater overall survival) in two studies. On the other hand, the hypoexpression of miRNA-15a[26], miRNA-29b[12], miRNA-124[13], miRNA-129-5p[17], miRNA-199b-5p[4], miRNA-200b[21,25], miRNA-204[20], miRNA-20[18] and miRNA-218[6] was associated to the worst prognosis in nine studies, and miRNA-210[24] hypoexpression was associated with better prognosis in a single study (Table 2).

miRNAs associated with disease-free survival

Hyperexpression of miRNA-21[10], miRNA-370[15] and miRNA-711[5] was associated with lower disease-free survival in three studies, while miRNA-339-5p[19] hyperexpression was associated with greater disease-free survival in a single study. On the other hand,

Table 2. Expression of miRNAs associated with prognostic aspects.

Prognostic aspect	Hypoexpressed miRNAs	Hyperexpressed miRNAs
Lymph node metastasis	miRNA-124[13], miRNA-127[16], miRNA-129-5p[17], miRNA-199b-5p[4], microRNA-206[18], miRNA-218[6] and miRNA-339-5p[19]	miRNA-21[14], miRNA-301a[11] and miRNA-370[15]
Distant metastasis	miRNA-204[20] and miRNA-200b[21]	
Tumor size	miRNA-29b[12] and miRNA-129-5p[17]	miRNA-21[22,23] and miRNA-301a[11]
Tumor phenotype (TN)	miRNA-21[23]	miRNA-210[24] and miRNA-301a[11]
Overall survival		
Poor survival	miRNA-15a[26], miRNA-29b[12], miRNA-124[13], miRNA-129-5p[17], miRNA-199b-5p[4], miRNA-200[21,25], miRNA-204[20], miRNA-206[18] and miRNA-218[6]	miRNA-21[10], miRNA-301a[11] and miRNA-711[5]
Best survival	miRNA-210[24]	miRNA-127[16] and miRNA-339-5p[19]
Disease-free survival		
Poor survival	miRNA-15a[26], miRNA-29b[12] and miRNA-204[20]	miRNA-21[10], miRNA-370[15] and miRNA-711[5]
Best survival	miRNA-210[24]	miRNA-339-5p[19]
Estrogen receptor		
Positive		
Negative	miRNA-200b[25]	miRNA-21[22]
Progesterone receptor		
Positive		
Negative	miRNA-129-5p[17]	miRNA-21[10]
HER-2		
Positive	miRNA-200b[25]	miRNA-21[22]
Negative		

TN: triple negative.

hypoexpression of miRNA-15a[26], miRNA-29b[12] and miRNA-204[20] was associated with lower disease-free survival in three studies, while miRNA-210[24] hypoexpression was associated with greater disease-free survival in a single study (Table 2).

DISCUSSION

The studies evaluated in this systematic review have shown that tumor miRNAs are useful biomarkers to predict the prognosis of breast cancer patients. Analysis of its expression allowed to differentiate characteristic expression profiles in this cancer in relation to normal mammary tissue and the expression of miRNAs in breast cancer was also correlated with conventional prognostic characteristics, such as tumor size, lymph node metastasis, distant metastasis and lower survival , suggesting the potential prognosis of these biomarkers.

The miRNAs can be investigated in two ways, either in tumor tissues or in circulating form, in serum or plasma. In this study, we prioritized the miRNAs evaluated in tumor tissues compared to normal tissues. The miRNAs may be hyper- and hypoexpressed in tumor tissues. Hyperexpressed ones can act as oncogenes because of their ability to suppress tumor suppressor genes[8]. The major oncogenic miRNAs were miRNA-21[10,14,22,23], miRNA-301a[11], miRNA-370[15] and miRNA-711[5] and their hyperexpression was associated with more aggressive characteristics of the tumor. In contrast, hypoexpressed microRNAs may act as tumor suppressors, as long as they suppress the expression of oncogenes[8]. Tumor suppressor miRNAs included miRNA-339-5p[19], miRNA-206[18], miRNA-204[20], miRNA-127[16], miRNA-200b[21,25], miRNA-15a[26], miRNA-29b[12], miRNA-124[13], miRNA-129-5p[17], miRNA- 199-5p[4] and miRNA-218[6], and the hypoexpression of most of these was associated with the presence of lymph node metastasis.

In the present study, miRNA-21 and miRNA-200b were the most commonly investigated in the prognosis of breast cancer. The miRNA-21, considered as an oncogenic miRNA, was investigated in four studies and its expression was significantly increased in breast cancers compared to normal tissues. Hyperexpression of this miRNA was significantly associated with more aggressive tumor characteristics, such as larger tumors and lymph node metastasis. Patients with breast cancer with hyperexpression of miRNA-21 presented worse prognosis, that is, lower overall survival[10,14,22,23].

The miRNA-200b, considered a tumor suppressor, was investigated in two studies and its expression was significantly lower in breast cancers than in normal tissues. The hypoexpression of miRNA-200b was associated with the most advanced clinical stage and the presence of distant metastases in breast cancer. Patients with miRNA-200b hypoexpression presented worse prognosis compared to those with overexpression of miRNA-200b[21,25].

Other miRNAs were also associated with the prognosis of breast carcinomas, but most of them were evaluated in only one study. The lowest survival rates were associated with hyperexpression of miRNA-301a[11] and microRNA-711[5] and hypoexpression of miRNA-15a[26], miRNA-29b[12], miRNA-124[13], miRNA-129-5p[17], miRNA-199b-5p[4], miRNA-204[20], miRNA -206[18] and miRNA-218[6]. On the other hand, higher survival rates were associated with the hyperexpression of miRNA-127[16] and miRNA-339-5p[19] and also to the hypoexpression of miRNA-210[24]. Thus, these miRNAs can be considered as having the most promising prognostic potential for breast cancer.

The findings of this study were similar to those found in three systematic reviews available in the literature. Nassar et al.[27] demonstrated that miRNA-21, miRNA-210 and miRNA-711, when hyperexpressed, were associated with lower survival rates. Other miRNAs suggested as prognostic biomarkers were reported by this study, including miRNA-9, miRNA-30a, let-7b, miRNA-106b, miRNA-122, miRNA-18b, miRNA-103, miRNA-107, miRNA-652, miRNA -155, miRNA-19a, miRNA-181b, miRNA-24, miRNA-27a, miRNA-27b-3p, miRNA-23a, miRNA-324-5p, miRNA-122, miRNA-375, miRNA-126, miRNA-10a. Van Schooneveld et al.[28] also reported miRNA-21 and miRNA-210 as associated with poor prognosis in breast cancer. Bertoli et al.[29] reported that miRNA-21, miRNA-29b, miRNA-204, miRNA-210 and miRNA-339-5p are the major prognostic biomarkers for breast cancer.

A discordant point to our systematic review over those previously published is that many miRNAs that appear in the other reviews were not included in our study. It is important to emphasize the heterogeneity of the previously published reviews, which evaluated the expression of miRNAS not only in tumor tissues, but also in blood, serum or plasma of patients with breast cancer. In addition to the diversity of biological samples evaluated, some included studies analyzing the expression of miRNAs in cell lines and not in tumor tissues or that used different quantification methods, such as microarrays and ***in situ*** hybridization.

Some limitations should be considered when interpreting the results of the present study. First, the analysis was limited to articles published in English. Second, the large number of miRNAs evaluated in individual studies makes it difficult to validate the results and to conduct qualitative and quantitative analyses, as a meta-analysis.

It is likely that the use of miRNAs as prognostic biomarkers has important implications for predicting the survival of breast cancer patients and that they will be incorporated as a new tool in clinical practice in the future. However, the results emphasize the need to systematically validate these findings in additional independent cohorts or through preclinical/clinical verification studies. In addition, it is necessary to select the most relevant miRNAs in breast cancer and to carry out global studies with a greater number and diversity of patients. In this way, the miRNAs can be used in clinical practice.

CONCLUSION

Specific tissue miRNAs can be considered as promising new biomarkers for prognosis in breast cancer patients. In this review, the expression of miRNAs associated with the prognosis of breast carcinomas was demonstrated. However, our results emphasize the need to systematically validate these findings in additional studies so that miRNAs are incorporated as a new tool in clinical practice.

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