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CONTENTS

EDITORIAL

173 **Why is breast cancer early detection important?**
Por que a detecção precoce do câncer de mama é importante?
Sandra Gioia

ORIGINAL ARTICLES

176 **Local re-operation and recurrence in oncoplastic breast surgery**
Reoperação e recidiva local em cirurgia oncoplástica mamária
Vanessa Amoroso, Cicero Urban, Rubens Silveira de Lima

182 **Trends and attitudes toward oncoplastics training in Mastology in Brazil**
Tendências e atitudes para o treinamento oncoplástico em Mastologia no Brasil
Cícero Urban, Orivaldo Gazoto Júnior, Douglas Miranda Pires, Guilherme Novita Garcia, Regis Resende Paulinelli, Vanessa Amoroso, Ruffo Freitas Júnior

187 **Impact of preoperatory magnetic resonance imaging in oncoplastic surgery**
Impacto da ressonância magnética pré-operatória na cirurgia oncoplástica
Karina Furlan Anselmi, Cicero Urban, Linei Urban, Ana Paula Martins Sebastião, Rubens Lima, Flavia Kuroda, Cleverton Spautz, Thiago Astorga Martins, Iris Rabinovich, Eduardo Schunemann

194 **Impact of the pink october in the mammographic screening adherence in a reference center in oncology**
Impacto do outubro rosa na adesão ao rastreamento mamográfico em um centro de referência em oncologia
Poliana Ruhmke Vazzoller, Yuri Costa Farago Fernandes, Bruna Aparecida Gotardo, Jocelito Ruhnke, Douglas Soltau Gomes

199 **Androgen receptor expression in triple negative breast cancer and its relationship to prognostic factors**
Expressão de receptor de androgênio em câncer de mama triplo negativo e sua relação com fatores prognósticos
Maximiliano Cassilha Kneubil, Alessandra Eifler Guerra Godoy, Guilherme Portela Coelho, Rafael Grochot, Renato Luis Rombaldi, Fábio Firmbach Pasqualotto, Bruno Wensing Raimann, José Mauro Madi, André Borba Reiriz, Mariana Alessi, Nathalia Hoffmann, Mariana Roesch-Ely, Janaína Brollo

206 **The validity of an adjustable compression Velcro wrap for the treatment of patients with upper limb lymphedema secondary to breast cancer: a pilot study**
Validação de uma vestimenta de contenção para tratamento de linfedema de membro superior secundário ao câncer de mama: estudo piloto
Larissa Louise Campanholi, Graziele Chiquette Lopes, Fábio Postiglione Mansani, Anke Bergmann, Jaqueline Munaretto Timm Baiocchi

213 **Frequency and factors associated with injury to the axillary vein in women that underwent axillary lymphadenectomy during breast cancer surgical treatment**
Frequência e fatores associados à lesão da veia axilar em mulheres submetidas à linfadenectomia axilar no tratamento cirúrgico do câncer de mama
Rafaela Miranda Corrêa, Danila Pinheiro Hubie, Reitan Ribeiro, José Clemente Linhares, Sérgio Bruno Bonatto Hatschbach

220 **Association between alcohol consumption and breast cancer development: a case-control study**
Associação entre ingesta alcoólica e desenvolvimento de câncer de mama: um estudo de caso-controle
Laís Franciele Santana Portela, César Augusto Costa Machado, Renata Costa Cangussú, Luciana Castro Garcia Landeiro, Susanne de Andrade Blanc Bertrand, Rebecca Meireles de Oliveira Pinto

225 **Correlation between ultrasonographic features and histopathological findings of breast lesions in biopsies**
Correlação entre características ultrassonográficas e achados histopatológicos de lesões mamárias em biópsias
Laila Carolline Freitas e Silva, Josmara Ximenes Andrade Furtado

230 **Alteration of bone mineral density in breast cancer female survivors on chemotherapy treatment: an integrative review**
Alteração da densidade mineral óssea em mulheres sobreviventes de câncer de mama tratadas com quimioterapia: revisão integrativa da literatura
Larissa Vaz Gonçalves, Sara Socorro Faria, Jordana Carolina Marques Godinho Mota, Karine Anusca Martins, Ruffo Freitas-Junior

237 **Assessment of female sexual function and quality of life among breast cancer survivors who underwent hormone therapy**
Avaliação da função sexual e da qualidade de vida de mulheres sobreviventes do câncer de mama submetidas a hormonioterapia
Ana Beatriz Gomes de Souza Pegorare, Keslyn da Rosa Silveira, Ana Paula Simões No, Susi Rosa Miziara Barbosa

245 **Paget's disease of the breast: study of cases series**
Doença de Paget na mama: estudo de uma série de casos
Walberto Monteiro Neiva Eulálio Filho, Flávia Vanessa Carvalho Sousa Esteves, Taíla Sousa de Moura Fé, Luan Barbosa Furtado, Raimundo Gerônimo da Silva Junior, Sabas Carlos Vieira

CASE REPORTS

249 **Breast reconstruction using expander and fat grafting after mastectomy associated to radiotherapy**
Reconstrução mamária com o uso de expansor e lipoenxertia após mastectomia associada a radioterapia
Bruno Bohrer Flores, Maria del Rosario Sarmiento Piñeres, Roberto José da Silva Vieira, Carlos Ricardo Chagas, Gabriela Volkart Pinho

253 **Idiopathic granulomatous mastitis: diagnosis and follow-up with magnetic resonance imaging**
Mastite granulomatosa idiopática: diagnóstico e seguimento com ressonância magnética
Felipe Eduardo Martins de Andrade, Rebeca Neves Heinzen, Kátia Maciel Pincerato, Fábio Arruda de Oliveira, Marcos Fernando Docema, Carolina Rossi Saccarelli, Alfredo Carlos Simões Dornellas de Barros

CONSENSUS MEETING

258 **Breast cancer screening: updated recommendations of the Brazilian College of Radiology and Diagnostic Imaging, Brazilian Breast Disease Society, and Brazilian Federation of Gynecological and Obstetrical Associations**
Recomendações do Colégio Brasileiro de Radiologia e Diagnóstico por Imagem, da Sociedade Brasileira de Mastologia e da Federação Brasileira das Associações de Ginecologia e Obstetrícia para o rastreamento do câncer de mama
Linei Augusta Brolini Dellê Urban, Luciano Fernandes Chala, Selma di Pace Bauab, Marcela Brisighelli Schaefer, Radiá Pereira dos Santos, Norma Medicis de Albuquerque Maranhão, Ana Lucia Kefalas, José Michel Kalaf, Carlos Alberto Pecci Ferreira, Ellyete de Oliveira Canella, João Emílio Peixoto, Heverton Leal Ernesto de Amorim, Helio Sebastião Amâncio de Camargo Junior

I **INSTRUCTIONS TO AUTHORS**

EDITORIAL
DOI: 10.5327/Z259453942017EDIT273

WHY IS BREAST CANCER EARLY DETECTION IMPORTANT?

Por que a detecção precoce do câncer de mama é importante?

Sandra Gioia[1]*

On June 15 of the current year, the Brazilian Society of Mastology – Rio de Janeiro Region (SBM/RJ) promoted a discussion on public health policies in breast cancer at the VII International Symposium on Mastology – Rio (SIM Rio). There was a seminar addressing the barriers and strategies for the implementation of the guidelines for the early detection of breast cancer in Brazil.

Strategies for the early detection of breast cancer and rapid access to treatment were discussed. Such factors are essential for the decrease in mortality and the increase in breast cancer survival rates. The event allowed for democratic participation, ensuring transparency and promoting learning opportunities for both interest groups and the audience, with the use of evidence-based knowledge.

The event was attended by managers from all government levels, supporters from breast cancer-related technical areas, researchers interested in the translation processes of scientific knowledge, and the Brazilian and international civil society. Decisions considered urgent were exposed through common dialogue and points of convergence, transcending conflicts of interest. These decisions represent direct contributions to assist public health policies in breast cancer not only in Rio de Janeiro, but in the whole country.

With this meeting, the SBM/RJ achieved its main objective, which was to promote integration and to show that together, we can develop outstanding and quality work. This quality is an attribute to be always sought in an organized, collective and synergistic way, unlike what is observed in the daily life of health services, in which individuals do what they consider most appropriate, but without the desired result.

We have to strive to do the right thing at the right time and in the right way. Our actions are not to be seen as a punctual obligation or the fulfilling of a meaningless requirement. In relation to the seminar on barriers and strategies to implement the guidelines for the early detection of breast cancer in Brazil, I present the following considerations:

Early detection of breast cancer requires the early diagnosis in women with symptoms of the disease and, in addition, may include screening asymptomatic women. Both efforts should consider the cultural context of the community in question, the resources available to support the program and the sustainability of those efforts over time[1]. Effective early detection programs may lead to decreased staging, which increases the proportion of breast cancers detected at an early stage, when treatment is most effective[1].

Noncommunicable diseases, such as cancer, are overcoming infectious diseases as one of the most pressing health care threats in low – and middle-income countries[2]. By 2025, 59% of all new cancer cases and 68% of deaths caused by cancer will occur in these countries[3]. Consequently, local health systems are struggling to respond to this change in this scenario[4].

Breast cancer represents a major public health problem in the world and in Brazil. In 2015, it was the most prevalent cancer (with 2.4 million new cases) and the leading cause of cancer deaths[5]. In Brazil, breast cancer is the most common malignant neoplasm and the leading cause of death among women, with 14,206 deaths in 2013, and 57,960 new cases estimated for 2017[6]. Barriers to accessing cancer care in Brazil lead to delays in diagnosis and treatment, with consequent advanced stages at presentation and a high mortality rate[7].

In medium – and low-income countries, long delays for diagnosis and treatment often lead to clinical progression of the disease. In the United States, 60% of breast cancers are early diagnosed, whereas in Brazil, this is true for only 20% of cases[2].

Even within Brazil, staging and survival statistics vary according to sociodemographic characteristics, such as the type of health insurance plans[8-11]. Women treated in the Brazilian public health system (*Sistema Único de Saúde*– SUS) present with a more advanced stage of the disease than those who have follow-up in the private sector, and public sector patients have worse disease-free and global survival rates (which may be partially attributed to greater delay and advanced stages at the time of diagnosis)[8-10].

In the health area, many guidelines or recommendations for disease management are developed, especially those directed to the improvement of daily routines of professionals in health systems. Dissemination and implementation of these recommendations are often focused on professionals, not on patients[12]. As a result, in many countries, patients are not aware of such guidelines and are not able to access the publications, or do not fully understand academic and medical terminologies[13].

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Since the 1980s, Brazil has followed a course of actions for breast cancer prevention and control. It was after this period that the first initiatives to face cancer as a health problem of great magnitude emerged, suggesting that the spread of the disease should be contained by a planned governmental action[14]. This transitional moment was responsible for the implementation of actions, activities, programs and policies to control breast cancer, which resulted in the preparation of the Guidelines for the Early Detection of Breast Cancer in Brazil in 2015[15]. This last publication is part of a set of actions developed by the Brazilian Ministry of Health with the purpose of expanding and qualifying the early detection of breast cancer, aiming to reduce the mortality caused by this disease, but still finds many barriers to its implementation.

Screening for breast cancer progresses in the SUS, with a modest level of mammography coverage, regional inequalities and low adherence to technical guidelines. We consider it necessary to strengthen early diagnosis (training of professionals, timely investigation and access to treatment). Also, to value the educational work with women so that they know more about the problem and forms of prevention, become familiar with their breasts and adopt a careful attitude about the suspected changes that suggest breast cancer[16]. Regardless of the efforts of public agencies and the Brazilian medical community, breast cancer indicators such as staging, survival and mortality rates remain below the expected level[16].

The identification of barriers and strategies to implement the national guidelines policy for the early detection of breast cancer in Brazil is necessary in an attempt to change the current scenario. The investigation of the literature aiming at the search for evidence that identifies how other health systems deal with the overcoming of barriers is important for the proposal and application of the improvement of this policy in Brazil, especially within the SUS.

- We have a big problem to be solved. Although breast cancer control needs a multidisciplinary effort, it is well known that mastologists should assume their responsibility as care coordinators.
- I invite you all to reflect on your work practices and to share responsibility for the management of breast cancer patient care, be that in a micromanagement, mesomanagement or macromanagement level: from self care, caring for families and communities, care offered in services, care offered in integrated health systems, care policy formulation, and even the search for *innovative financial instruments*. This is because everything has a cost and, if we wait for the underfunded SUS, we will never reach the long-awaited result: to reduce cancer mortality in Brazil. By organizing and presenting sensible, robust projects, with indicators of achievement, we will find financing sources to perform our activities with quality.
- To minimize the chaos installed we immediately need to:
  - offer dignity to health system users, removing barriers and eliminating bureaucracy with attention to the human being and not the disease itself, transforming the disease regulatory system into a patient follow-up system. The Patient Navigation Program proposes to bring diagnosis and treatment in a timely manner to our so complex and yet fragmented SUS[17]. It can be customized for each region of Brazil and act in areas of promotion, prevention, diagnosis, treatment, rehabilitation and palliative care[18];
  - empower users and primary health care professionals, taking advantage of the wave of implementation of the Family Health Strategies (FHS). They will be our helping hands. The study led by researchers at Imperial College London, in collaboration with the data integration center at Fiocruz (CIDACS), found that a better level of governance and greater health coverage in primary care in Brazilian municipalities are associated with reduced mortality[19]. And the FHS may be the beginning of our long-awaited organized screening;
  - develop the feeling of *nonconformity* in mastologists who are in their "castle of knowledge" and to stop passively "accepting" the so common advanced stage lesions. Let's be the *connecting point* that the Health Care Network of our locality needs;
  - optimize the diagnostic poles of suspected lesions, whether palpable or not, for case resolution. In order to boost the organization of secondary care, in 2014, Ordinance no. 189 was published, which established financial incentives for costing and investment for the implantation of Reference Services for Diagnosis of Breast Cancer (SDM)[20]. The ordinance defined criteria for the habilitation of health units, in addition to the minimum number of exams necessary for diagnosis;
  - learn to be organized in order to generate and interpret quality health care management data. There is no other way out! We have to use health information technology;
  - It is of no importance to diagnose if you have no place for quality treatment. Investments in early detection are important, but timely and appropriate treatment based on scientific evidence is crucial;
  - we need to find our inspiring muse: a national personality who with beauty, charisma and determination shows doctors that they are not gods and that we have much to learn about the female universe. We sometimes forget that there are cultural and psychological barriers to demystification. I believe that engaging actresses and artists with high penetration into society would solve many of our problems with early detection. A doctor may reach dozens of patients, but a muse can reach millions of women.

Words teach, but examples lead others to knowledge. Let's be an example of good medical practice and let's get out of our comfort zones... many lives need to be saved. And, for the future, I think we have to work with educational actions in schools. We have to

educate our children. I believe that this type of action should gain more attention. They may change the current scenario, something we have not been able to achieve in decades. They can also transform many other things socially, economically, politically and culturally.

I quote an excerpt from the book *Focus*, by Daniel Goleman:

At the service of what exactly are we using whatever our talents are? If our focus only serves our personal goals – self-interest, immediate reward, and our inner circles – in the long run, we are all, as a species, condemned... Is it true just for me, or it is also for others? Is it for the benefit of a few, or of many? Is it for now, or for the future?

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LOCAL RE-OPERATION AND RECURRENCE IN ONCOPLASTIC BREAST SURGERY

Reoperação e recidiva local em cirurgia oncoplástica mamária

Vanessa Amoroso[1], Cicero Urban[1,2]*, Rubens Silveira de Lima[2,3]

ABSTRACT

Introduction: In addition to a surgical option, the oncoplastic surgery (OP) is a new philosophy in the mammary oncologic therapy, since it combines concepts of oncologic surgery and plastic surgery. There was a concern that plastic surgery techniques would compromise the oncologic radicalism, leading to an increased risk of tumor recurrence and damage to the patients' survival. The main purpose of the breast conservative surgery (BCS) is to obtain disease-free surgical margins, with a great esthetic-functional result. However, since the advent of this approach, the search for negative margins has been a problem. Despite the efforts to avoid compromised margins, they occur in 20 to 40% of the cases in the traditional BCS, and in many cases leading to the need of re-excision or even to mastectomy. **Objective and method**: In the analysis of recent studies, the OP role as a reduction factor of new surgeries and local recurrence is questioned. The aim of this paper is to analyze it based on literature review. **Conclusion**: According to recent studies, the OP became a safe oncological surgical technique that improves both the esthetic result and the disease local control, decreasing the compromised margins with impact on the mitigation of new surgeries rate.

KEYWORDS: Mammoplasty; Local recurrence of neoplasia; Reoperation; Margins of excision; Segmental mastectomy.

RESUMO

Introdução: A cirurgia oncoplástica (OP) além de opção cirúrgica é uma nova filosofia no tratamento oncológico mamário, pois combina os princípios da cirurgia oncológica com os da cirurgia plástica. Existia um temor de que as técnicas de mamoplastias redutoras pudessem comprometer a radicalidade oncológica, levando a um risco aumentado para recidivas tumorais e prejuízo na sobrevida das pacientes. O objetivo primário da cirurgia conservadora de mama (CC) é obter margens cirúrgicas livres de doença, com bom resultado estético-funcional. Entretanto, desde o advento dessa abordagem, a busca por margens negativas tem sido problemática. Pois, apesar do esforço para se evitar margens comprometidas, elas ocorrem em 20 a 40% dos casos na CC tradicional, levando, em muitas situações, à necessidade de reexcisão ou até mesmo mastectomia. **Objetivo e método**: Analisando estudos recentes, questiona-se o papel da OP como um fator redutor de reoperações e recidiva local. O objetivo desse artigo é fazer uma discussão embasada em revisão da literatura. **Conclusão**: Conforme estudos recentes, a OP consagrou-se como técnica cirúrgica oncologicamente segura, com melhora tanto no resultado estético como no controle local da doença, diminuindo margens comprometidas e impactando na atenuação da taxa de reoperações.

DESCRITORES: Mamoplastia; Recidiva local de neoplasia; Reoperação; Margens cirúrgicas; Mastectomia Segmentar.

Study carried out at Hospital Nossa Senhora Das Graças – Curitiba (PR), Brazil.
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INTRODUCTION

An oncoplastic surgery (OP) is considered a well-conducted tumor resection followed by immediate breast reconstructive surgery, which evaluates the symmetry with the contralateral breast in the same surgery[1,2]. In addition to a surgical option, this is a new philosophy in the mammary oncologic therapy, since it combines concepts of oncologic surgery and plastic surgery. There was a concern that plastic surgery techniques would compromise the oncologic radicalism, leading to an increased risk of tumor recurrence and damage to the patients' survival. However, contrarily to this initial concern, a combination of mammoplasty techniques to mammary oncologic surgery showed to be positive. It could even add safety regarding margins, and at the same time reduce the risk of a poor esthetic-functional result[1].

OP techniques are more complex and require more time than the traditional conservative surgery (BCS). From the oncologic, aesthetic, and psychological point of view, the selection of patients is essential[3]. Some points are crucial for the obtainment of satisfactory results, among which:

- proper surgery to resect each type of tumor;
- immediate reconstruction using the proper techniques; and
- handling of contralateral breast[4].

Several factors may influence the decision of the surgical technique that will be used, such as obesity, diabetes, smoking habits, autoimmune diseases and previous radiotherapy. Essentially, obesity, smoking habits, and previous radiotherapy may cause an increase in the number of complications, regardless of the adopted technique. Obesity may increase the rate of complications in 12 times. Smoking habits may also interfere due to the vasoconstrictor effect. It reduces blood flow in the capillary through inhibition of catecholamine measured by nicotine, thus increasing the chances of necrosis in tissue flaps. Previous radiotherapy may change tissue vascularization due to fibrosis, which may also be accompanied by healing disorders. Although diabetes as an isolated factor does not increase the complication rates, its impact is seen when associated with obesity or previous radiotherapy, increasing the rates of infection and cutaneous necrosis[5].

There are indications established for the OP, which include mammary resection with a volume higher than 20% and patients with macromastia, in which the result of a skin-saver mastectomy technique is not satisfactory. Relative contraindications are the following:

- extensive tumors located in the medial breast region;
- small mammary volume or with no ptosis;
- previously irradiated breasts;
- smoker patients or those with decompensated diabetes; and
- patients with excessive or disproportional expectations regarding the esthetic result[3].

There are several reduction mammoplasty techniques that may help in the BCS. Reductive mammoplasty based on a superior vascular pedicle consists of a mammary reduction with periareolar and vertical scar (which may also include horizontal scar in T), also known as Lejour or Pitanguy technique. It may be used in cases of tumors located in the lower quadrants, and an average or large volume breast is necessary, with a minimum of ptosis. Reductive mammoplasty based in the changed lower vascular pedicle is based on the inferoposterior areolar vascular pedicle, and it may be applied to tumors located in the upper quadrants of the breast[6]. Double vascular pedicle mammoplasty is a technique combining vascular pedicle for the areola and a lower glandular vascular pedicle. This technique is especially indicated for cases of very superficial tumors located in upper-external quadrants, which need a tumor resection with skin margin[6]. Mixed pedicles for excisions out of the area commonly used in breast reduction techniques may allow for tumor resections in almost any place of the breast[7]. Periareolar techniques, such as the round-block ones, allow resections in all quadrants and are most indicated for small or average volume breasts with minimum or moderate ptosis.

Evaluation of oncologic efficacy is done based especially on the overall survival, disease-free survival, and disease local control rates through local recurrence rates[2]. The OP is an innovative methodology. However, it needs further studies comparing different surgical techniques and evaluating oncologic and repairing results in a more objective way[2,8-10].

LOCAL RECURRENCE AND RE-OPERATING RATE

The majority of local recurrence appears in the initial tumor site, which indicates that it derives from residual tumor cells. Compromised margins require a new subsequent operation to avoid remaining tumor cells, which may lead to a new mastectomy, depending on each case[11]. Therefore, the surgical margin status is a critical factor for the disease local control[12].

The determining factors for local control were considered to be the tumor size, the presence or not of metastasis in axillary lymph nodes, and hormonal receptors status (estrogen and progesterone). However, with the new concepts of tumor biology, the determining factors are currently more related to the molecular biology of the tumor and adjuvant therapy than with the size of the resection margin. Such concept was popularized as "bigger is not better" [13,14].

Factors such as histological degree, components of noninvasive carcinoma, lobular histology, and multicentricity are predictive of conservative surgery failure and conversion to mastectomy[14].

There are countless risk factors associated with a high rate of new surgeries due to compromised margins. Among which, we may point out the following:

- tumor size;
- tumor multifocality;
- extensive *in situ* component; and
- increased mammary density showed through mammography[11].

There is also the factor associated with regional variations in histopathological definitions:

- margins status;
- capacity of imaging and locating non-palpable tumors;
- 3D perception of the tumor by the surgeon; and
- desire to keep a good esthetic result[15].

Systemic treatments reducing the incidence of distant metastasis also decrease the risk of local recurrence[13].

Previous studies showed a local recurrence rate in five years (60 months) after the OP varying from 8.5 to 9.4%. Most literature reviews have an average time of follow-up (average of 4.5 years) with a local recurrence rate ranging from 0 to 1.8% per year[16] (Table 1).

Although the purpose of a new surgery is to reduce the risk of local recurrence and the mortality, its actual benefit remains undetermined, since approximately 50% of new surgeries do not show a residual tumor in the anatomopathological test, creating doubt about its real need, as it does not change the mortality rate[17]. Similarly, although the OP allows for a larger resection of the tumor and reduces the compromised margin rates, its value in the local recurrence still needs to be confirmed[16,18].

There is a lack of standardization and protocols on the approach and handling of compromised margins among surgeons, despite the significant psychological, physical, and financial effects of re-excision in the patients[17].

ONCOPLASTIC SURGERY AND SURGICAL MARGINS

The primary purpose of BCS is to obtain disease-free surgical margins, with an excellent esthetic and functional result. However, since the advent of this approach, the search for negative margins has been a problem. Despite the efforts to avoid compromised margins, they occur in 20 to 40% of the cases in the traditional BCS, and in many cases leading to the need of re-excision or even to mastectomy[19,20]. This is associated with an increase in the therapy cost and the morbidity, and delay to begin adjuvant therapies[13,17].

The OP showed to be effective in several series (Table 1), allowing larger excisions and keeping the effective local control rates. Since the mammoplasty techniques involve flaps rotation and displacement of the mammary glandular tissue, the concern with surgical margins is essential, considering that if a second surgery is needed to extend them, this may be even more complex[21-23]. In a systematic review from Piper et al. (2016), the new surgery rate in the OP was of 3.5% and the mastectomy rate was 3.7%. When the OP is compared with the traditional BCS, the new surgery rates are lower and the mastectomy rates are equivalent. Thus, the reductive mammoplasty allows larger tumor resections, resulting in an improvement of the margins control[23].

Among the pathology laboratories, there is a lack of standardization in the processing of samples, especially in the accuracy of the microscopic margins evaluation, which subsequently creates a difficulty to study the effect of millimetric differences between the margins size[13,14].

The consensus of the Society of Surgical Oncology (SSO) and from the American Society for Radiation Oncology (ASTRO) emphasizes the importance in reaching free-tumor margins

Table 1. Literature series comparing oncological results in patients treated with oncoplastic breast surgery.

Author/year	Rate of compromised margins (%)	Number of patients	Average follow-up time (months)	Distant metastasis rate (%)	Re-operating rates (%)	Local recurrence rate (%)	Rate of mastectomies (%)
Kaur et al. (2005)	16	-	-	-	-	-	-
Rietjens et al. (2007)	3	148	74	13	-	3.4	-
Munhoz et al. (2009)	5.5	218	-	-	-	-	-
Meretoja et al. (2010)	16.2	90	26	3.3	-	8	-
Fitoussi et al. (2010)	18.9 (comprometidas ou exíguas)	540	49	-	-	6.8	9.4
Hamdi (2013)	2.5	119	48	-	-	1.7	-
Haloua et al. (2013)	0-10	998	74	-	-	-	3- 16
Losken et al. (2014)	12	3116	37	-	4	4	6.5
Kaviani et al. (2014)	5	258	26	3.3	-	2.9	-
Rezai et al. (2015)	-	944	62	-	-	4	7.2
De Cruz et al. (2016)	9.8	6011	50.5	8.7	-	3.2	-
De Lorenzi (2016)	-	454	86.4	9.9	-	7.5	-

to optimize local control, and they highlight that no tumor cells touched the dye (in invasive carcinomas and *in situ*) as a negative criterion. This is based on the Houssami et al. (2014) meta-analysis outcomes, which showed that margins of one, two, or five millimeters were not associated with different risks for local recurrence[14,24]. This fact corroborates the results of the clinical trial from the American College of Surgeons Oncology Group (ACOSOG), which provides more evidence on the concept that, in this current era of multiple therapies, minimizing the subclinical tumor margin is not essential to reduce local recurrence. Therefore, the concept that the resection margin of invasive carcinoma should have from two to five millimeters should be abandoned. Hopefully, this will bring a decrease in the re-excision rates. This is also in line with the concept of the negative margin from the National Surgical Adjuvant Breast and Bowel Project (NSABP), which is no tumor cell touching the dye[25].

When the OP is associated with the intraoperative evaluation of the margins, there is an even higher decrease in the new surgery rates, if compared to traditional BCS[23]. Intraoperative evaluation of the margins provides a safe resection of the tumor, minimizing possible surgeries to extend the resection margins[21].

Intraoperative techniques commonly used in the margins evaluation are the following:

- freezing;
- cytology;
- intraoperative ultrasonography; and
- sample radiography.

They all present limitations, and no specific technique has become universal in the international practice up to now. Pathological anatomy techniques are operator-dependent; therefore, they need resources and usually have a slow response. Only some sample points may be used for freezing, and the tissue may suffer from artifacts. Cytology techniques do not allow distinguishing one *in situ* tumor from an invasive tumor, and they do not provide information on the sample edge. Intraoperative ultrasonography is also operator-dependent, requires specific training, and suspected calcifications may not be visualized. Sample radiography is not capable of detecting noncalcified lesions, and benign calcification may be wrongly interpreted as malign[15,26]. Among them, the intraoperative evaluation technique of higher accuracy margins, according to St. John et al. (2016) meta-analysis, is freezing (sensitivity of 86% and specificity of 96%), along with cytology[15].

Some oncoplastic series in the literature are summarized in Table 1. Kaur (2005) obtained in his comparative study between the OP and traditional BCS a 16% rate of compromised margins with the OP, while the compromised margins rate in the BCS technique was of 43%[27]. Rietjens et al. (2007), in a retrospective cohort study of 148 patients subjected to bilateral OP, found a compromised margins rate of 3%[6]. In the series of Munhoz (2009), 218 patients subjected to OP were evaluated, and 5.5% of them showed positive resection margins in the final pathologic evaluation by paraffin, that is, a false-negative of the assessment through margins freezing[26]. In the series of Meretoja (2010), a compromised margins rate of 16.2%[28] was showed.

In the retrospective study of Fitoussi (2010), with an average follow-up of 59 months, the low or compromised margins rate was of 18.9%[29]. In the series of Hamdi (2013), with 119 patients subjected to the OP, a 2.5% rate of margins compromised by the tumor was obtained[30]. In 2013, in the systematic review of Haloua et al., the rate of compromised margins in the group treated with BCS ranged from 20 to 40%. Use of OP resulted in a rate of 78 to 93% of tumor-free margins and compromised margins, ranging from 0 to 10%, leading to the mastectomy need in 3 to 16% of all OP cases[19].

In the series of Kaviani (2014), 258 patients were included, all subjected to OP and prospectively followed-up, and in 95% of the cases, free margins were obtained[31]. At Losken (2014) meta-analysis, the compromised margins rate was significantly lower in the group treated with OP (12 *versus* 21% of the group treated with BCS; $p<0.0001$)[18].

In 2015, in the study of Rezai et al., in only 7.2% of the cases there was a need of later mastectomy (associated with multicentricity, large tumor size, and repeatedly undetermined margins). In addition, the lobe histological types, multicentricity, and multifocality are predictive factors of a subsequent mastectomy, although there is no impact on the overall survival[32]. In 2016, in the De Cruz's systematic review, the compromised margins rate was of 9.8%[9].

ONCOPLASTIC SURGERY AND THE *IN SITU* CARCINOMA

The increase in early detection of breast cancer, due to tracing with mammography, lead to an increase in the incidence of ductal carcinoma *in situ* (DCIS), which corresponded to an average of 20% of all breast tumors. It should be ensured that there are no residual tumor cells, and at the same time, there must be a concern on removing the smallest margin possible to minimize breast deformities. There is no evidence that larger margins provide better rates of the disease local control[33].

Currently, radiotherapy is the gold standard in therapy after BCS for DCIS[33]. Randomized studies evaluating the breast conservative post-surgery radiotherapy in DCIS therapy found high levels of local recurrence, with half of them being diagnosed as invasive carcinomas. The local recurrence rates in patients with DCIS treated with BCS range from 26 to 36% in those not treated with radiotherapy; from 9 to 23% in those treated with adjuvant radiotherapy – according to randomized prospective studies with 13 to 20 years of follow-up[34].

There are no randomized prospective series in literature with groups including only patients with DCIS that evaluate the oncoplastic surgery. Only in one descriptive and retrospective Polish study from Szynglarewicz (2016), a series of 36 patients diagnosed with DCIS treated with the reductive mammoplasty techniques was described, in which a new surgery rate of 8.3% was seen in patients showing near margins (1 mm or less)[35].

CONCLUSION

In the analysis of recent studies, the OP role as a reduction factor of new surgeries and local recurrence is questioned. According to recent studies, the OP became a safe oncological surgical technique that improves both the esthetic result and the disease local control, decreasing the compromised margins with impact on the mitigation of new surgeries rate.

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TRENDS AND ATTITUDES TOWARD ONCOPLASTICS TRAINING IN MASTOLOGY IN BRAZIL

Tendências e atitudes para o treinamento oncoplástico em Mastologia no Brasil

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ABSTRACT

Introduction: There is a growing interest in, and an increasing demand for, oncoplastic (OP) and reconstructive surgery training by breast surgeons. However, until now there has been a lack of a specific model for training in this field in most countries and no data with respect to learning curves. Mastology has been a medical specialty in Brazil since 1978. It is fully dedicated to studying, preventing, diagnosing, and managing all diseases of the breast. Incorporation of OP and reconstructive surgery in Mastology presents a number of challenges, and there are some controversial issues to overcome. **Objective:** The purpose of this study, therefore, was to analyze how OP and reconstructive techniques are being incorporated into surgical training in Mastology in Brazil. **Methods:** A specific survey was designed to cover all surgical residents who concluded their regular program in Mastology in Brazil in 2015 and 2016. **Results:** One hundred twenty-four residents from 49 breast units were included, with the majority having their training for all 2 years of their residence, as recommended by the Brazilian Society of Mastology. In addition, most of the respondents were able to perform partial breast reconstructions and reconstructions using expanders and implants, but 20% of them had a lack of specific training in these techniques. **Conclusion:** As adequate local control of disease and quality of life are related to surgical decisions, it is expected that breast surgeons expand their limits and responsibilities in order improve the reality of most breast cancer patients.

KEYWORDS: Breast reconstruction; oncoplastic surgery; education, medical; breast neoplasms.

RESUMO

Introdução: Existe um interesse e uma demanda crescente de treinamento oncoplástico (OP) e cirurgia reconstrutiva por cirurgiões de mama. No entanto, até agora tem faltado um modelo específico de treinamento neste campo na maioria dos países, sem dados com relação à curva de aprendizado. A Mastologia tem sido uma especialidade médica no Brasil desde 1978. É totalmente dedicada a estudar, prevenir, diagnosticar e gerenciar todas as doenças da mama. A incorporação de OP e cirurgia reconstrutiva na Mastologia apresenta uma série de desafios, e há algumas questões controversas a serem superadas. **Objetivo:** O objetivo deste estudo, portanto, foi analisar como a OP e as técnicas reconstrutivas estão sendo incorporadas no treinamento cirúrgico em Mastologia no Brasil. **Métodos:** uma pesquisa específica foi projetada para cobrir todos os residentes cirúrgicos que concluíram seu programa regular em Mastologia no Brasil em 2015 e 2016. **Resultados:** Foram incluídos 124 residentes de 49 unidades mamárias, com a maioria treinada durante todos os 2 anos de residência, conforme recomendado pela Sociedade Brasileira de Mastologia. Além disso, a maioria dos entrevistados foi capaz de realizar reconstruções e reconstruções mamárias parciais usando expansores e implantes. Mas ainda 20% deles apresentaram falta de treinamento específico nestas técnicas. **Conclusão:** uma vez que o controle local adequado da doença e da qualidade de vida está relacionado às decisões cirúrgicas, espera-se que os cirurgiões de mama ampliem seus limites e responsabilidades para melhorar a realidade da maioria dos pacientes com câncer de mama.

PALAVRAS-CHAVE: Reconstrução mamária; cirurgia oncoplástica; educação médica; neoplasias de mama.

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INTRODUCTION

Surgical management of early breast cancer includes partial and total reconstruction in order to achieve appropriate tumor extirpation and minimize deformities. Poor cosmetic outcomes and asymmetry after breast cancer surgery can lead to fear of death, a loss of femininity and a decline in the quality of life[1]. In order to meet these needs, oncoplastic surgery (OP) is now part of surgical training and competency in Mastology in Brazil.

Although OP was pioneered by European surgeons, particularly in France and Germany, there are breast surgeons in Brazil who started performing these techniques in the 1980s. In addition, the field of Mastology, as a medical specialty in Brazil, has experienced an increasing interest from breast residents, fellows and specialists ("mastologists") in OP over the past 15 years.

However, the incorporation of OP techniques in Mastology presents a number of challenges and controversial issues. One of these issues is the lack of a specific model for OP training. In addition, some controversies remain in many countries about whether it is better to have breast surgeons and plastic surgeons working together, or a breast specialist doing everything in most, or indeed in all, cases. Also, surgical mentoring is a significant challenge for all specialties[2-16]. The delivery of qualified OP and reconstructive training is expected to be tailored as to meet educational needs and to be recognized internationally.

The purpose of this study, therefore, was to analyze how OP techniques are being incorporated into surgical training in Mastology, in Brazil, and to address potential concerns for the better training of future specialists in breast surgery.

METHODS

A specific survey was designed by the authors to assess the current surgical training in OP in Mastology in Brazil. The questionnaire had 25 multiple-choice items and it was disseminated to all surgical residents who concluded their Mastology program in Brazil in two consecutive years (2015 and 2016). The survey was anonymously applied just before their test for being approved as specialists by the Brazilian Society of Mastology. The surveys were then collected and exported to Microsoft Excel©. All completed surveys were analyzed using IBM SPSS statistical software for Windows, version 20.0 (SPSS, Chicago, IL). Multiple-choice scales were analyzed as ordinal variables. Bivariate analyses using Pearson's χ^2 were carried out in order to analyze the categorical data obtained from the research and to compare the residents' answers about which professional was responsible for the training of breast surgeons in each institution, whether plastic surgeons or mastologists. All results found to be statistically significant, with a two-sided alpha error of <0.05, were further analyzed by calculating crude *odds ratios* (OR) and 95% CI, which allowed the identification of demographic determinants of attitudes towards training in OP.

RESULTS

In Brazil, there are 49 breast units accredited by the Brazilian Society of Mastology and by the Brazilian National Committee for Residence Training to provide specific training in Mastology. Each year, more than 60 residents attend these programs. This study included 124 residents who concluded their training in Mastology in 2015 and 2016. All but two of the residents responded to this survey, and the characteristics of those with valid surveys and their related breast units are listed in Table 1. Table 2 shows how

Table 1. Characteristics of breast units and Medical Residents who concluded their surgical training in Mastology in Brazil in 2015–2016.

Characteristic	n (%)
Sex	
Male	37 (29.8)
Female	87 (70.2)
Number of new breast cancer cases/year in the Breast Unit where the resident was trained	
50–100	7 (5.6)
101–200	23 (18.5)
201–300	27 (21.8)
>300	67 (54.8)
Who is in charge of breast reconstructions in the Breast Unit?	
Mastologist	25 (20.1)
Plastic surgeon	49 (39.5)
Mastologist and plastic surgeon (both perform breast reconstructions)	50 (40.3)

Table 2. Characteristics of oncoplastic and reconstructive surgeries in Mastology' residents breast unit.

Characteristics of the breast reconstructions in the Breast Unit	n (%)
% of immediate breast reconstructions after mastectomies	
<10%	18 (14.5)
10–20%	31 (25.0)
20–50%	27 (21.8)
>50%	48 (38.7)
How most of breast reconstructions after mastectomy are done?	
Mostly with expanders/implants	105 (84.7)
Mostly with pedicle flaps	18 (14.5)
Mostly with microsurgical flaps	1 (0.8)
% of breast conserving surgeries with oncoplastic techniques	
<10%	30 (24.2)
10–20%	26 (21.0)
20–50%	35 (28.2)
>50%	33 (26.6)

breast reconstructions are carried out in Mastology residence training, in Brazil.

Three different realities, in terms of surgical training in OP, emerged from this survey. Most Mastology residents did their training in OP for the whole period of residence. Besides, around 20% of residents had been in specific stages in Plastic Surgery Departments for 3 months, and around 20% did not have access to these stages or only had minimal contact with these techniques (Figure 1).

Table 3 shows what residents feel able to do after 2 years of surgical training in Mastology in comparison to those who are performing OP and reconstructive surgery in the unit.

DISCUSSION

New generations of breast surgeons should now be oncoplastic surgeons. In other words, oncoplastic surgeons are specialist breast surgeons. While the controversy about whether breast or plastic surgeons should perform breast reconstruction is still present in some countries, the breast is an aesthetic-functional organ, and surgeons who perform breast surgeries should always consider aesthetic outcomes in all their procedures. It is expected that even those breast surgeons who work together with plastic surgeons will perform better surgeries if they incorporate skills in plastic surgery of the breast.

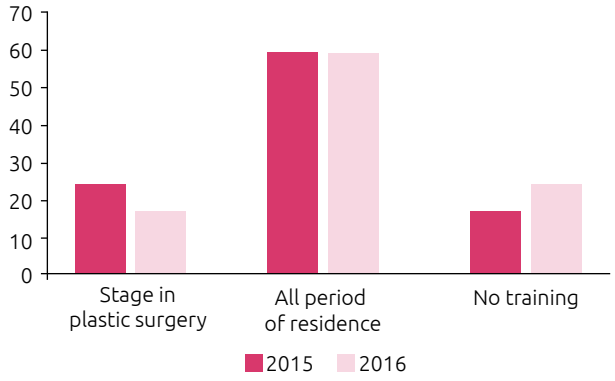

Figure 1. Breast Surgeons Training in Oncoplastic Surgery in Brazil in 2015 and 2016.

However, until now, there is a lack of a specific model for training in OP in most countries, and no data with respect to learning curves. In Brazil, Mastology has been a medical specialty since 1978. It is fully dedicated to studying, preventing, diagnosing, and managing all diseases of the breast. There are 2 years of specific residence training, which is completed after 2 or 3 years in General Surgery or Gynecology. During this period, the medical resident attends an educational program approved by the Brazilian Society of Mastology and by the Brazilian National Committee for Residence Training, carried out in 49 different institutions (both public and private). There are specific stages in their regular training regarding radiology, pathology, medical and radiation oncology, and surgery (benign, oncologic, reconstructive and aesthetics ones).

Traditionally, breast cancer surgeries have been performed in many countries by general surgeons/surgical oncologists or gynecologists, together with plastic surgeons when breast reconstruction is recommended. In some countries, however, breast surgeons carry out the majority of OP and reconstructive surgeries. In the United Kingdom, for example, general surgery trainees undertake OP during their last 3 years of specialty rotations, which can be supplemented by a one-year fellowship in a highly competitive National Training Interface Group[7]. There are several potential advantages to the development of the breast surgeon specialist with OP and reconstructive skills. There are many places in Brazil, as the big country it is, with just a few plastic surgeons available to provide reconstructive surgeries for all patients in need. Fully trained OP breast surgeons would be able to carry out more extensive resections and avoid some unnecessary mastectomies, achieving symmetry intraoperatively[13].

The survey highlighted the fact that, when a breast surgeon is in charge of breast reconstruction (alone or in collaboration with a plastic surgeon), the Mastology resident has better training in all levels of skills in OP and reconstructive techniques than those

Table 3. What the resident in Mastology is able to do in oncoplastic and reconstructive surgery at the end of their training, according to who is in charge of breast reconstruction in the breast unit.

Technique	Breast Surgeon does Reconstruction (n=75)	Plastic Surgeon does Reconstruction (n=47)	P
Partial reconstruction	66 (88%)	15 (32%)	<0.0005
Expander/implants	58 (77%)	5 (11%)	<0.0005
Latissimus dorsi	31 (41%)	3 (6%)	<0.0005
TRAM	11 (15%)	1 (2%)	0.028
Breast reduction	46 (61%)	5 (11%)	<0.0005
Augmentation mammoplasty	40 (53%)	4 (9%)	<0.0005

TRAM: transverse rectus abdominis myocutaneous.

who were trained in breast units where there are no breast surgeons performing breast reconstructions[3]. This phenomenon is probably related to some controversies between the specialties of Mastology and plastic surgery, which have not yet been resolved in Brazil. It was also shown that most residents are able to do partial reconstructions and reconstructions with expanders and implants. In an ideal situation, both specialties could, together, contribute to the better education of breast and plastic surgery residents. In Brazil, a discrepancy between private and public health practice has been noted due to the lack of a populational mammographic screening program[17,18]. As a consequence, public health care institutions more often have more advanced cases than private ones. Indications and techniques of reconstruction can vary as well as the levels of training.

In the United States, where breast surgery is not a medical specialty, breast diseases comprise 14–25% of general surgeons' practice by volume. Nearly half of all general surgeons perform only two or fewer breast cases per month. Unquestionably, survival is linked to performance measures. For instance, survival is greater if surgeons perform more than 15 breast cancer operations per year. Breast-focused surgeons, according to an editorial by Pass, Klimberg and Copeland III, are more competent[8]. It is worth noting that most Mastology residents are trained in breast units with large numbers of new breast cancer cases and that breast reconstruction is a major element in most of these cases, indeed being performed in most of them.

However, there are controversial issues to be resolved between breast and plastic surgeons regarding boundaries and who should be in charge of OP and reconstructive surgery. Future directions for the training of mastologists/breast surgeons and plastic surgeons should include exchange of experiences, which would be very positive for both specialties and for patients. There is a growing interest in, and an increasing demand for, OP and reconstructive surgery in the field of Mastology in Brazil, as well as for breast surgeons around the world. The challenge will be to deliver qualified OP and reconstructive training, both theoretical and practical, which can be tailored to meet educational needs and also be internationally recognized. The avoidance of errors is essential, which requires training in early recognition and the ability to deal with complications.

Finally, it will be regarded the issue of competence. Conceptually, competence can be defined as being both physically and intellectually adequate or well qualified for a given activity. Breast surgeons should be well trained and competent in all aspects of breast oncology and have broad understanding of breast defects and all their reconstructive requirements, as well as being proficient in prevention and providing care for all potential complications. This is the challenge for present and future mentoring of breast surgeons [3-16]. Adequate local control of disease and quality of life are both deeply related to surgical decisions and skills at the moment of breast cancer diagnosis and treatment. This means breast surgeons must expand their limits and responsibilities in order to improve the reality of most breast cancer patients.

CONCLUSION

The Brazilian program for OP and reconstructive training in Mastology demonstrates an appropriate efficacy regarding educational environment in most breast units. However, this is only a starting point to identify and further develop standards for OP and reconstructive training and credentials at international level.

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IMPACT OF PREOPERATORY MAGNETIC RESONANCE IMAGING IN ONCOPLASTIC SURGERY

Impacto da ressonância magnética pré-operatória na cirurgia oncoplástica

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ABSTRACT

Objective: There is no data about magnetic resonance image (MRI) impact in oncoplastic surgery (OP). The objective of this study was to evaluate the impact of MRI on the surgical planning and the changes of conduct in patients with initial breast cancer and candidates to perform the OP. **Methods:** This is a prospective cohort of 60 patients who were candidates to OP between January 2013 and July 2014. All of them underwent to a preoperative MRI, in addition to mammography (MG) and ultrasound (US). Any additional tumor in the MRI classified as BIRADS 4-5 were biopsied or marked with carbon and radiotracer in order to be localized during the surgery. Surgical impact of additional MRI findings were evaluated as to changes of approach to mastectomy or to wider resection. **Results:** Of the patients, 29/60 (48.3%) had additional findings on MRI, 16/29 (55%) were multifocal tumors, 1/29 (3.4%) was multicentric, 5/29 (17%) were contralateral tumors, and 9/29 (31%) presented tumor size larger than 10 mm in the MRI. Of 22 patients who showed additional lesions on MRI, 15 (68.2%) had invasive carcinomas in the definitive anatomopathological exam. Sensibility of MRI was higher in the estimation of the tumor size. Of the patients, 12/60 (20%) underwent to mastectomy, and 17/60 (28.3%) to wider resections. Only 5% of patients had positive margins in the entire group, and in the group of patients that had additional findings on MRI only 3.4% had positive margins. **Conclusions:** MRI is better than MG and US in evaluating the extension of the tumor, and in the detection of multicentricity, multifocality and bilaterality. In consequence, it contributed in this series for a better surgical planning in OP with a low rate of compromised margins and re-operations.

KEYWORDS: Breast cancer; magnetic resonance imaging; surgery.

RESUMO

Objetivo: Não há dados sobre o impacto da imagem de ressonância magnética (RM) na cirurgia oncoplástica. O objetivo deste trabalho foi avaliar o impacto da RM no planejamento cirúrgico e nas mudanças de conduta em pacientes com câncer de mama inicial e candidatas a realizar a cirurgia oncoplástica. **Métodos:** Trata-se de uma coorte prospectiva de 60 pacientes que foram candidatas à cirurgia oncoplástica entre janeiro de 2013 e julho de 2014. Todos elas foram submetidas a uma RM pré-operatória, além de mamografia (MG) e ultrassom (US). Qualquer tumor adicional na RM classificada como BIRADS 4-5 foi biopsiado ou marcado com carvão e ROLL para serem localizados durante a cirurgia. O impacto cirúrgico dos achados adicionais da RM foi avaliado quanto a mudanças para mastectomia ou ressecção mais ampla. **Resultados:** Das pacientes, 29/60 (48,3%) apresentaram achados adicionais na ressonância magnética, 16/29 (55%) foram tumores multifocais, 1/29 (3,4%) foi multicêntrico, 5/29 (17%) foram tumores contralaterais e 9/29 (31%) apresentaram tamanho de tumor maior que 10 mm na RM. Das 22 pacientes que apresentaram lesões adicionais na RM, 15 (68,2%) apresentaram carcinomas invasivos no exame anatomopatológico definitivo. A sensibilidade da RM foi maior na estimativa do tamanho do tumor. Das pacientes, 12/60 (20%) foram submetidas à mastectomia e 17/60 (28,3%) a ressecções mais amplas. Apenas 5% das pacientes apresentaram margens positivas em todo o grupo. No grupo de pacientes que apresentaram resultados adicionais na RM, apenas 3,4% tiveram margens positivas. **Conclusões:** A RM é melhor que a MG e o US na avaliação da extensão do tumor e na detecção de tumores multicêntricos, multifocais e bilaterais. Em consequência, contribuiu nesta série para um melhor planejamento cirúrgico na cirurgia oncoplástica com baixa taxa de margens comprometidas e reexcisão.

PALAVRAS-CHAVE: Câncer de mama; imagem por ressonância magnética; cirurgia.

Study carried out at Unidade de Mama do Hospital Nossa Senhora das Graças – Curitiba (PR), Brazil.
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INTRODUCTION

Mastectomy was considered the standard treatment for oncoplastic surgery (OP) until the early 1970s, when randomized clinical trials showed equivalence in terms of long-term survival and local control of the disease with breast-conserving treatment (BCT)[1,2]. However, BCT has shown high re-operation rates in some recent series[3,4]. Thus, accuracy on the local preoperative staging is considered essential for better planning the techniques that should be applied in each individual case. Clinical exam, mammography (MG) and ultrasound (US) correspond to the triad traditionally used for this end.

OP combines the principles of plastic surgery with those of surgical oncology, and represents quite an advance in BCT[5]. The aim of it is to preserve the quality of life of patients with surgeries that can be efficient from the oncologic point of view without compromising the aesthetic-functional outcomes. Besides that, it reduces the risk of compromised margins, when compared to traditional BCT techniques. Nevertheless, accuracy of imaging methods is essential to the surgical planning, mainly concerning the choice of pedicles, incisions and techniques for symmetry in the contralateral breast.

Several studies have shown the high sensitivity of magnetic resonance (MRI) to evaluate tumor extension, multifocality and multicentricity[6-34]. However, there are some controversies concerning the application of MRI as a method of preoperative staging in BCT, as it increases eligibility to mastectomies. In addition, some criticism toward the preoperative MRI use in the routine of BCT sustain that many of the additional lesions might not have any clinical or biological relevance, or even that they could be treated in a more effective way through radiotherapy instead of more aggressive surgeries[35].

Therefore, this study aimed to evaluate the sensitivity, specificity and the impact of MRI on surgical planning in patients with breast cancer eligible to OP.

METHODS

Sixty patients were included in this prospective single-arm cohort study. All of them had invasive breast cancers T1-T2, or ductal carcinoma in situ (DCIS), with the age ranging between 25 and 80 years old. All patients were evaluated and diagnosed through clinical exam, MG, US and breast biopsy (core-biopsy or vacuum-assisted biopsy). They were clinically eligible to undergo BCT with OP techniques at the Breast Unit of Hospital Nossa Senhora das Graças (HNSG) in Curitiba (Brazil) between January 2013 and July 2014. After the diagnosis, the patients underwent MRI. All results were evaluated by the same radiologist (LU), who has full dedication to breast imaging and ten years of experience in breast MRI. Additional lesions at MRI classified as BIRADS 3 were not considered for surgical resection. Such patients were followed-up every six months for a period of two years, whenever the lesion has not been resected in the mammoplasty area. Additional lesions detected in MRI classified as BIRADS 4 were biopsied or marked both with radioactive tracer and carbon under MRI guidance or had a second-look on the US, then resected during the surgery. BIRADS 5 lesions were biopsied during the preoperative stage. In order to be included in this study, additional lesions detected through MRI had to be as large as, or larger than, 5 mm.

Patients excluded from this study were those with locally advanced or metastatic disease at initial diagnosis, those who underwent MRI prior to the diagnosis, those who chose mastectomy despite being eligible to BCT, those undergoing neoadjuvant chemotherapy, those who had previous oncological treatment for other cancers, and those with contraindication or allergy to the MRI contrast or claustrophobia.

Magnetic Resonance Imaging

MRI exams were performed with a 1.5 T (Avanto®, Siemens) equipment, having patients in prone position, with a 16-channel RF coil. The contrast used had a dose of 0.2 mL/Kg Omniscan® (Gadolineo, GE Healthcare), with a 3 mL/s infusion pump. Other exam protocols included pondered sequences in T2 (axial plane) and STIR (sagittal plane), followed by a 3D dynamic sequence pondered in T1 with a fat saturation (axial), and immediate reconstruction with subtraction (one pre-contrast sequence and four post-contrast sequences, at a rate of 90 seconds/acquisition and 7 minutes total time). The dynamic sequence was followed by a high-resolution 3D acquisition pondered in T1 with fat saturation (sagittal) for reconstruction. After that, all exams were sent to a workstation (Carestrean Health), where the radiologist evaluated the morphology and the dynamic behavior of the lesions, classifying them according to the current BI-RADS® system. All additional lesions underwent a second-look ultrasound and, once any abnormality was found, a core-biopsy was also performed. In case no abnormality was found in the second-look ultrasound, they underwent percutaneous vacuum-assisted biopsy (Mamotomme®) or preoperative marking with radiotracer and activated carbon 4% guided through MRI (Breast Biopsy®, Avanto, Siemens). All mammograms and ultrasounds were reviewed by the same radiologist (LU), in order to compare them to the MRI.

Pathology

A pathologist fully dedicated to breast pathology (APMS) did at least three methods for intraoperative margins and sentinel node assessment: gross, touch imprint and frozen sections. Each surgical specimen had their margins properly marked by the surgical team with colored buttons, and with complete radiological and clinical data information. The whole specimen had been inked and thinly sliced. Margins were considered negative when cancer cells do not touch inked surface. The tumor size measurements for the final report were assessed on gross for

tumors larger than 20 mm and through microscopy for tumors smaller than 20 mm. Additional lesions detected through MRI (all of them marked with carbon) were evaluated by the pathologist as to their size and whether they were invasive carcinoma or DCIS, or even benign or atypical lesions.

Oncoplastic surgery techniques

The OP techniques used in this series were: inferior and superior pedicle, and round-block. In cases in which the surgical plan changed to mastectomy, patients underwent skin-sparing mastectomy or nipple-sparing mastectomy, according to the risk of compromising nipple and areola complex, with immediate reconstruction with definitive form-stable anatomical implants.

Statistical analysis

In order to analyze whether the differences between tumor sizes, measured by means of three distinctive methods (MRI, US and MG), were representative, a Friedman's test with a posteriori Dunn's test was applied. Besides that, in order to check if the tumor size measured through the anatomopathological exam after the surgery was different from the one measured on the MRI, a Wilcoxon's test was used. In order to analyze the association between a change of approach by the patient and the tumor size on the MRI and on the anatomopathological exam, as well as the association between a change of approach and the several variables, a Mann-Whitney's test was applied; also the χ^2 distribution or Fisher's exact test was applied, depending on whether the variable was quantitative or qualitative. The same tests were used in order to evaluate the association between the change of approach in the group of women with additional lesion, as well as in the group of women that underwent mastectomy, after taking MRI. Non-parametrical analyses were used whenever the variables studied failed Shapiro-Wilk's normality test. The statistical analyses was performed with GRAPHPAD PRISM's statistical package, which is considered as level of significance at 5% (α=0.05)[36,37].

Ethical aspects

This study was approved by the Internal Review Board from Positivo University.

RESULTS

Sixty patients were included in this prospective cohort. The characteristics of the population can be found in Table 1. Twenty-nine (48.3%) patients showed additional findings considered suspect for malignancy in the same breast or in the contralateral breast, and/or tumor size larger than the one studied on the MG and on the US, exceeding 10 mm of difference on MRI (Table 2). Among the additional findings in the MRI, 16/29 (55.2%) were multifocal tumors, 1/29 (3.4%) were multicentric

Table 1. Characteristics of the patients eligible to oncoplastic surgery and undergoing preoperative magnetic resonance imaging.

Characteristics	n (%)
Age – in years	54.7±10.6
Menopausal condition	
Pre-menopause	24 (40.0)
Post-menopause	36 (60.0)
Family history	
Positive	10 (16.7)
Negative	50 (83.3)
T	
Tis	2 (3.1)
T1	44 (67.7)
T2	19 (29.2)
BMI	
Underweight	1 (1.6)
Normal weight	27 (45.0)
Overweight	20 (33.0)
Obesity	12 (20.0)
Breast size	
Small	7 (11.7)
Medium	22 (36.7)
Large/Extra large	31(51.7)
Histological type	
Ductal invasive carcinoma	36 (60%)
Ductal carcinoma in situ	3 (5.0)
Lobular invasive carcinoma	13 (21%)
Others	8 (13%)
Angiolymphatic invasion	
Present	18 (30.5)
Absent	42 (69.5)
N	
0	44 (78.0)
1	13 (22.0)
Estrogen receptor	
Positive	53 (89.8)
Negative	7 (10.2)
Progesterone receptor	
Positive	49 (81.4)
Negative	11 (18.6)
HER2	
Positive	6 (10.2)
Negative	54 (89.8)
Not researched	4 (6.2)
Ki67	
<15%	35 (58.4)
>15%	25 (41.6)

BMI: Body Mass Index; T: Primary tumor size; N: Regional lymph nodes metastasis; HER2: Human Epidermal growth factor receptor 2; Ki67: Antigen KI-67.

tumors, 5/29 (17.2%) were tumors in the contralateral breast, and 9/29 patients (31.0%) had tumors sized larger than 10 mm on MRI, when compared with the MG and the US (Table 2). The MRI had higher sensibility to estimate the tumor size, when compared to the definitive anatomopathological exam, both on the comparison with tumors that could only be seen through MG or US and, in the same way, with those which were found through both MG and US (Table 3).

In the group that had additional lesions or differences in tumor size above 10 mm on MRI, the following results were found: 18/29 (62.1%) invasive ductal carcinomas, 5/29 (17.2%) invasive lobular carcinomas, 3/29 (10.3%) DCIS, 2 (6.9%) mucinous invasive carcinomas, and 1 (3.4%) tubular invasive carcinoma. As the secondary variables (age, body mass index (BMI), family history, menopausal condition, presence of angiolymphatic invasion and Ki 67>15%) were analyzed, no representative association between such variables and the detection of additional findings in MRI was found. When the tumors were classified as luminal, A, B, HER2 and triple negative, none of them was statistically significant for findings of additional lesions or for different tumor size on the MRI. All suspect additional tumors in MRI were marked with activated carbon and were localized on the definitive anatomopathological exam. Thus, from the 22 patients that showed additional lesions, 15 (68.2%) had invasive carcinomas confirmed through the anatomopathological exam.

From the 29 patients who showed additional lesions in MRI or tumor size exceeding 10 mm on the MRI, 12 (41.3%) had a change of approach to mastectomy, and 17 (58%) had larger resection using OP techniques, keeping the conservative approach. Twelve patients among the population studied (12/60) (20%) underwent mastectomy due to MRI findings, out of whom 3 (25%) underwent nipple-sparing mastectomy, 6 (50%) underwent skin-sparing mastectomy, 1 (8.3%) underwent bilateral skin-sparing mastectomy, and 2 (16.6%) underwent bilateral nipple-sparing mastectomy. Bilaterality appeared in 5% of the patients in this series, and it was detected only through MRI. Patients who underwent a better surgical planning for the conservative surgery were 17/60 (28.3%), with larger resections and immediate reconstruction using OP techniques, aiming to encompass the

Table 2. Additional results found only through magnetic resonance imaging in 60 patients with breast cancer eligible to oncoplastic surgery.

Additional finding through MRI	n (%)
Multifocality	16 (26.7)
Multicentricity	1 (1.7)
Difference in TS >10 mm when compared to MG and US	9 (15)
Tumor in the contralateral breast	5 (8.3)

MRI: magnetic resonance imaging; MG: mammography; US: ultrasound; TS: tumor size.

Table 3. Comparison of tumor size between magnetic resonance imaging, mammography, ultrasound and definitive anatomopathological exam in patients eligible to oncoplastic surgery.

Comparison between MRI and MG (n=41)		
Concordance	34 (82.9%) vs 25 (61.0%)	p=0.033
Underestimated	2 (4.9%) vs 10 (24.4%)	
Overestimated	5 (12.2%) vs 6 (14.6%)	
Comparison between MRI and US (n=53)		
Concordance	48 (90.5%) vs 38 (71.7%)	p=<0.001
Underestimated	2 (3.8%) vs 15(28.3%)	
Overestimated	3 (5.7%) vs 0	
Comparison between MRI and MG+US (n=60)		
Concordance	53 (88.4%) vs 42 (70%)	p=0.014
Underestimated	2 (3.3%) vs 12 (20.0%)	
Overestimated	5 (8.3%) vs 6 (10%)	

MRI: Magnetic Resonance Imaging; MG: mammography; US: ultrasound.

Table 4. Correlation between additional findings through magnetic resonance imaging and changes in surgical approach for patients eligible to oncoplastic surgery.

	Wider resection	Mastectomy	Contralateral mastectomy	Contralateral resection
Difference in TS> 10 mm on MR	8	1	0	0
Multicentricity	0	1	0	0
Multifocality	8	8	0	0
Contralateral breast lesion	0	0	3	2
Breast size				
S	1	3	1	0
M	3	4	2	1
L	11	2	0	1

TS: tumor size; MRI: magnetic resonance imaging; S: small; M: medium; L: large.

multifocal lesions or enlarging the resection for in case of patients that showed tumor size larger than 10 mm on the MRI (Table 4). Secondary variables, such as BMI, breast size, age, menopause, Ki 67>15%, family history, presence of angiolymphatic invasion and presence of positive sentinel lymph node, had no association with this group. When classified as luminal A, B, HER2 and triple negative, none of them was statistically significant too.

Among the 12 patients who underwent mastectomy, the eligibility to this procedure was due to the fact that, in 10 of them (83%) the lesions were multifocal, in 1 (8.3%) it was multicentric, and in 3 (25%) cancer in the contralateral breast was detected through MRI. As to tumor size, 6 (50%) patients who underwent mastectomy had tumors larger than 20 mm on the MRI exam. Considering the secondary variables among these patients, 4 (33.0%) had small size breasts, 6 (50%) had medium size breasts and 2 (16%) had large size breasts. As to family history, 5 (41.0%) of them had positive family history on the first-degree relatives for breast cancer. From the 12 mastectomies performed, 10 (83.3%) were considered eligible due to the lack of proportion between the breast size and the tumor size, added to the presence of multifocality and/or multicentricity, as well as positive family history (Table 5).

Only 3/60 (5%) patients had positive margins in the entire group, 3/48 (6.2%) exclusively in OP group, and in the group of 29 patients that had additional lesions on the MRI or tumor size larger than 10 mm on the MRI, only 1 (3.4%) had positive margins. The 2 patients that did not have additional lesions on the MRI and had positive margins were re-operated with OP techniques, and the only patient that had additional findings and positive margins was also re-operated with OP techniques (Figure 1). All of them had free margins and kept the conservative approach.

Table 5. Risk clinical findings leading to mastectomy in patients eligible to conservative surgery who underwent magnetic resonance imaging in the preoperative stage.

Variable	Mastectomy		P
BMI (kg/m²)			
Yes (n=12)	25.1±3,9		0.115
No (n=48)	27.6±5,2		
Age > 50 years			
Yes (n=34)	5	29	0.3319
No (n=26)	7	19	
Family history			
Yes (n=10)	5	5	0.021
No (n=50)	7	43	
Breast size			
Small (n=7)	4	3	0.016
Medium (n=22)	6	16	
Large (n=31)	2	29	
Menopause			
Yes (n=36)	5	31	0.1932
No (n=24)	7	17	
Ki67 > 15%			
Yes (n=26)	7	19	0.3358
No (n=33)	5	28	
AL invasion			
Yes (n=18)	6	12	0.156
No (n=41)	6	36	
Positive LS			
Yes (n=13)	3	10	0.711
No (n=46)	9	38	
Molecular classification			
HER2 (n=5)	2	3	0.556
Luminal A (n=32)	5	28	
Luminal B (n=19)	4	15	
Triple Negative (n=3)	1	2	
Tumor size AP			
T1	8	36	0.716
T2	4	12	

BMI: Body Mass Index; AL: Angiolymphatic invasion; LS: Sentinel lymph node; AP: Pathology; HER2: Human Epidermal growth factor receptor 2; Ki67: Antigen KI-67.

DISCUSSION

There are several studies comparing MRI with MG and US on the preoperative staging of patients with breast cancer. In most of them, the aim was to evaluate the MRI accuracy in the estimation

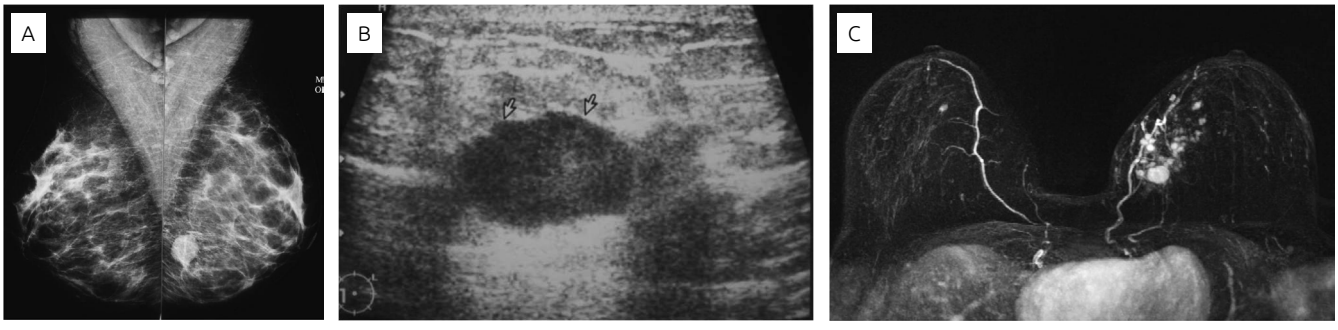

Figure 1. Example of a patient with distinct findings on mammogram, ultrasound and magnetic resonance imaging: (A) well delimitated breast mass, BIRADS 0 on mammogram; (B) solid mass, with indistinct margins, BIRADS 4; (C) additional tumors on magnetic resonance imaging in the same breast (multifocal tumor), and contralateral tumor, BIRADS 6.

of tumor extension and diagnosis of additional tumors in the same breast and/or in the contralateral one. Though none of them evaluated the MRI impact in OP, which is such an approach that allows to do larger resections in BCT[5-34].

In this prospective study, a rate of 48% (29/60) of additional findings was identified. The rates of multifocality, multicentricity and contralateral breast lesions in the 60 patients of our series were 26.7, 1.7 and 8.3% respectively. Houssami and Hayes, in a series with 2,610 patients, detected 40% of multifocal and multicentric tumors[31]. COMICE trial detected 16% of multifocal tumors[13]. The contralateral tumor rates found in our series were similar to other series[23,27-29].

From the additional lesions suspect of malignancy detected through MRI, 68% were positive on the anatomopathological exam. This is closer to the meta-analysis by Houssami et al., in which it was found 66%[21]. From the analyses of multifocal lesions, 58% were confirmed as malignant in the anatomopathological exam. The multicentric lesions and the lesions detected in the contralateral breast through MRI were 100% malignant in the anatomopathological exam.

It is not known whether additional tumors detected on MRI could be treated exclusively with adjuvant radiotherapy[31-33,35]. So, several studies reported a rate of change of surgical plan to mastectomy or to wider resections between 8.3 and 43%[18,19,23,24,28,30]. To our knowledge, this is the first study that refers to the impact of MRI on OP patients. After preoperative MRI, 20% of mastectomies and 80% of OP were performed in this group. And, among them, 28% had larger resections aiming to encompass multifocal lesions or larger tumors detected on MRI. In 52% of patients, the MRI had no impact on surgical decisions.

From 12 mastectomies in this series, 10 (83.3%) were due to the lack of proportion between the breast size and tumor size, added to the presence of multifocality and/or multicentricity, as well as positive family history. So, patients were referred to mastectomy not only due to the suspect additional findings on MRI. But, even for these cases, all patients had mastectomy skin-sparing or nipple-sparing with immediate breast reconstruction.

Considering the lesions that had over 10 mm in MRI, when compared to MG and US, the results were comparable to those found by Pengel et al.[19]. These authors demonstrated that the extension of tumor size is larger on MRI than on MG and US, as well as on the two associated exams. However, tumor size in MRI is more accurate when compared to definitive anatomopathological exam. Van Goethem et al. concluded that MG underestimates tumor size in 37%[20]. Our study confirmed that MG underestimated lesion size in 24% and that US did it in 28%.

The rates of positive margins and re-excisions were low in this series. From the 60 patients included here, the rate of positive margins was 5%, 6.2% in OP group (excluding patients who underwent mastectomy), and 3.4% in patients with additional findings on MRI.

CONCLUSION

There is still controversy with MRI in preoperative planning in breast cancer patients. However, the findings of this study have shown that MRI is more accurate than mammography and US in evaluating the extension of the tumor, in the detection of multicentricity, multifocality and bilaterality, thus contributing for a better surgical planning in OP. The consequence of that was a low rate of re-operations. Prospective and randomized trials are needed to confirm such findings.

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IMPACT OF THE PINK OCTOBER IN THE MAMMOGRAPHIC SCREENING ADHERENCE IN A REFERENCE CENTER IN ONCOLOGY

Impacto do outubro rosa na adesão ao rastreamento mamográfico em um centro de referência em oncologia

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ABSTRACT

Objective: To analyze the impact of Pink October in the mammographic screening adherence in a reference center in oncology. **Methods:** This is a cross-sectional, descriptive and retrospective study of a population of women who underwent mammographic screening in the years 2014, 2015 and 2016. Mammography reports were used for data collection. Comparing the months of October with the other months of the studied years, we observed if there were changes in the number of mammograms and in the proportion of mammograms Breast Imaging Reporting and Data System (BI-RADS) 3, 4 and 5. To verify statistical significance, the Z-score (95% confidence interval — CI95%) and the χ^2 test ($p<0.05$) were used. **Results:** 105,698 mammograms were performed. There was a significant difference in the number of mammograms performed in October compared to the other months of the study. In addition, there was an absolute increase in the number of mammograms BI-RADS 3, 4 and 5; however, their proportion in the months of October did not presented difference in comparison to the other months. **Conclusion:** Population-based campaigns to prevent breast cancer appear to be effective in increase of demand for mammographic screening, possibly leading to an increase in the number of cancers discovered, allowing more women to receive timely treatment.

KEYWORDS: Mammography; breast neoplasms; health promotion; mass screening; early diagnosis.

RESUMO

Objetivo: Analisar o impacto do Outubro Rosa na adesão ao rastreamento mamográfico para câncer de mama em um serviço de referência em oncologia. **Métodos:** Trata-se de um estudo transversal, descritivo e retrospectivo em uma população de mulheres que realizaram rastreamento mamográfico nos anos de 2014, 2015 e 2016. Foram utilizados laudos de mamografia para coleta de dados. Foram comparados os meses de outubro com os demais meses dos anos estudados, observando se houve alterações no número total de mamografias e no número de mamografias *Breast Imaging Reporting and Data System* (BI-RADS) 3, 4 e 5. Para verificar significância estatística foram utilizados o escore Z (intervalo de confiança de 95% – IC95%) e o teste do χ^2 ($p<0,05$). **Resultados:** Realizaram-se 105.698 mamografias. Houve diferença significativa na quantidade de mamografias efetuadas nos meses de outubro em comparação aos outros meses do estudo. Além disso, ocorreu aumento absoluto de mamografias BI-RADS 3, 4 e 5; porém, sua proporção nos meses de outubro não apresentou diferença significativa em relação aos outros meses. **Conclusão:** As campanhas populacionais de prevenção de câncer de mama parecem ser efetivas no aumento da procura por serviços de rastreamento, de forma a elevar o total de cânceres descobertos e possibilitando, assim, que mais mulheres recebam tratamento adequado.

PALAVRAS-CHAVE: Mamografia; neoplasias da mama; campanhas de prevenção de câncer de mama; programas de rastreamento; diagnóstico precoce.

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INTRODUCTION

Breast cancer is the most common type of carcinoma found among women worldwide, including Brazil, behind only skin non-melanoma ones. It corresponds to about 25% of new cases of cancer each year and is the fifth cause of death by neoplasia among the population in general and the main one among women[1]. In 2016, there was an estimation of 57,960 new cases of the disease, with an incidence of 56.2 cases every 100 thousand women[2].

Early detection is an important tool for a successful reduction in mortality[3,4]. The method of choice for screening is the mammography. Although the literature discusses the validity of populational mammography screening[5], institutions such as the Ministry of Health (MoH), the National Institute of Cancer (Instituto Nacional de Câncer — INCA)[6], the Brazilian Society of Mastology (Sociedade Brasileira de Mastologia — SBM), the Brazilian School of Radiology (Colégio Brasileiro de Radiologia — CBR), the Brazilian Federation of Gynecology and Obstetrics Associations (Federação Brasileira das Associações de Ginecologia e Obstetrícia — FEBRASGO)[7] and the U. S. Preventive Services Task Force (USPSTF)[8] recommend women are submitted to this procedure. Despite the different age range and periodicity recommendations, many test-age patients do not have access to the test or do not look for health care[9,10].

Information campaigns stand out among the motivations to seek for screening. In the United States of America, several states which would develop isolated actions for the screening of breast cancer got together for a unified awareness campaign on the disease. The pink ribbon became the symbol of the campaign called Pink October. The campaign was also adopted in Brazil with national relevance[11].

The objective of this study was to analyze the impact of Pink October in the adherence to mammographic screening for breast cancer in a reference oncology service in 2014, 2015 and 2016, observing changes in the total amount of mammograms performed and their impact on the proportion of mammograms diagnosed as classes 3, 4 and 5 Breast Imaging Reporting and Data System (BI-RADS) in October, when compared to other months of the year.

METHODS

It is a cross-sectional, descriptive and retrospective study in a population of women who underwent mammography in 2014, 2015 and 2016 at the mammography service of a hospital that is reference in oncology.

This study included all patients submitted to mammography in 2014, 2015 and 2016, according to a systematic verification of mammographic reports in electronic databases. The classification of the reports was given by the BI-RADS system[12]. Patients who couldn't have their BI-RADS determined were excluded from the study.

All mammograms were made in two mammography devices by MAMMOMAT 3000 Modular (Siemens), in standard incidences (craniocaudal and mid-lateral-oblique) and in complementary ones, when necessary[13]. The results were evaluated by the same radiologist.

Data collection was performed electronically with an Excel (Microsoft Office 2007, Brazil) spreadsheet, and elements were analyzed with QuickCalcs software (GraphPad Software Inc, La Jolla, CA, United States). The data selected were reported using a descriptive analysis. In order to evaluate whether the number of mammograms in the months of October was higher than the mean for other months in their respective years, we used the Z score, considering 95%CI (95% confidence interval) — values differing more than two standard deviation from the mean. The χ^2 test was used in order to evaluate whether the ratio for BI-RADS 3, 4 and 5 tests differed between October and other months of the year, considering statistical significance of $p<0.05$.

This work complied with the determinations from Resolution No. 196/1996 of the National Health Council (Conselho Nacional de Saúde — CNS), and was approved by the Research Ethics Committee of Centro Universitário Fundação Assis Gurgacz (CEP-FAG), No. CAAE 61718516.6.6.0000.5219.

RESULTS

The total of 105,698 mammograms were performed from 2014 to 2016: 33,197, in 2014, 36,392, in 2015 and 36,109, in 2016. The number of mammograms remained relatively stable, ranging from two to three thousand tests a month, except October, when peaks were observed. The amount of tests carried out in October was significantly higher (Z>+2) than in other months in their respective years. Moreover, the number of mammograms in November 2016 was also higher than the monthly mean of the same year (Z>+2) (Graphic 1).

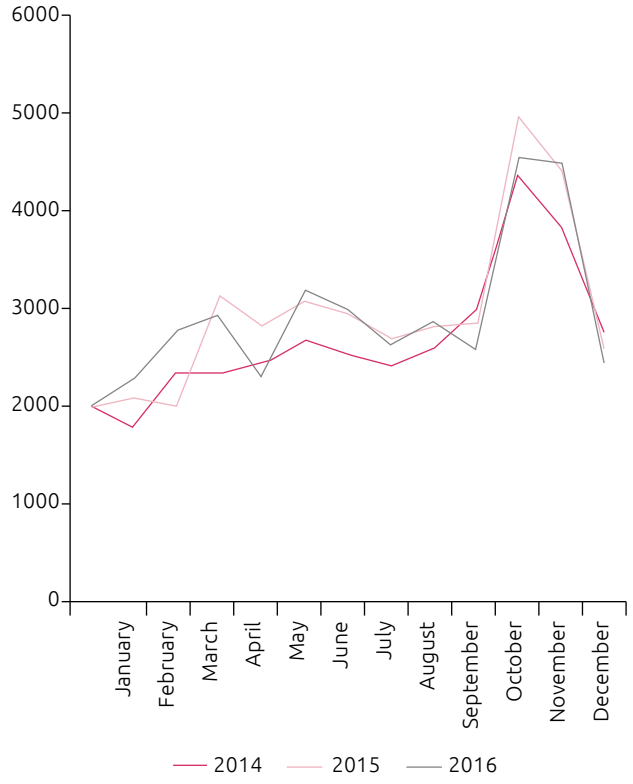
As for the tests classified as BI-RADS 3 (B3), it was observed that, in October 2014, there were 58 reports (11.95%), although the monthly mean of this year was of 40.4 B3 reports. In October of the following year, 65 tests (16%) were classified as such, with values higher than the monthly mean of 33.6 reports. In October 2016, 21 mammograms (8.82%) were B3, with a monthly mean of 19.8 tests in this category for the year.

In the first year of the study (2014), the month of October had 16 tests (12.9%) BI-RADS 4 (B4), while the monthly mean was of 10.3 reports. In 2015, the month of October had 14 B4 reports (9.27%), above the monthly average of 12.5 B4 mammograms. In the last year of the study, the month of October had 27 tests (17.08%) classified as B4 and had a monthly mean of 13.1 mammograms in this category.

In the case of tests classified as BI-RADS 5 (B5), in 2014, there were eight tests (15.6%) in the month of Pink October campaign and a monthly mean of 4.25 B5 results. In 2015, seven mammograms (11.1%) carried out in the month of October were B5, and

the monthly mean was of 5.25 reports. In 2016, the number of reports in category 5, carried out in October, was equal to the monthly mean for the year: four reports (8.3%).

In the month of October, 13,924 mammograms were carried out, of which 220 (1.58%) were classified as B3, B4 or B5, and 13,704 (98.42%) were classified as normal. In the other months studied, 91,774 mammograms were carried out, of which 1,428 (1.56%) were classified as B3, B4 or B5, and 90,346 (98.44%) were classified as normal. Despite the number of B3, B4 and B5 mammograms being higher in the month of October than in other months, no statistically significant difference was observed in the proportion of B3, B4 and B5 mammograms (p=0.43) (Table 1). In total, between 2014 and 2016, there were 1,648 tests classified as BI-RADS 3, 4 and 5 (Graphic 2).



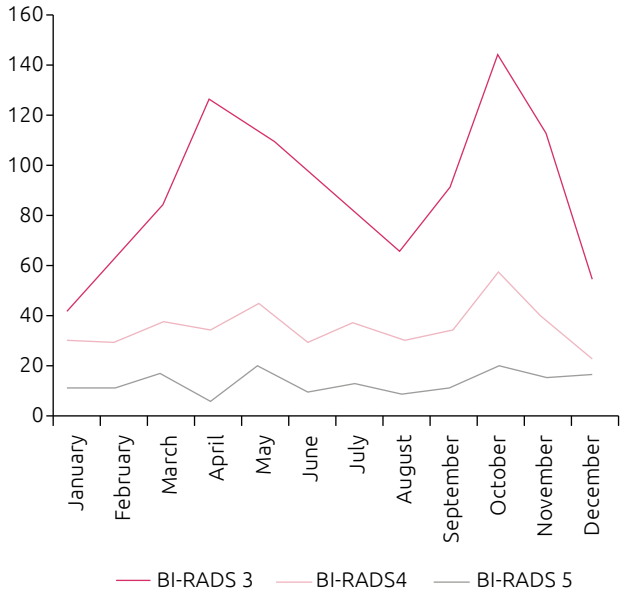
Graphic 1. Number of mammograms carried out monthly in a reference center in oncology: 2014, 2015 and 2016.

DISCUSSION

This study allowed analyzing the impact of Pink October on the adherence to the breast cancer screening in a reference service in oncology in 2014, 2015 and 2016.

A significant increase in the total of tests carried out in the month of October was observed in comparison to other months. This was possibly due to the effect of population awareness campaigns on breast cancer screening. Although results cannot be directly connected to Pink October — which could be done, for example, by using questionnaires on the motivation to join screening —, it is difficult to imagine other factors which lead to a consistent increase in the number of mammograms in October over three consecutive years. Thus, the present study is an indirect way to confirm the positive impact of Pink October in patient's search for screening.

The effect of the campaigns is estimated to be even greater than that demonstrated. The demand generated by the period of prevention campaigns results in the increased search that exceeds the structural capacity of the analyzed center. Therefore, many tests are scheduled not in October and are diluted in the following



Graphic 2. Number of Breast Imaging Reporting and Data System (BI-RADS) 3, 4 and 5 mammograms carried out monthly in years 2014, 2015 and 2016.

Table 1. Comparison between the proportion of Breast Imaging Reporting and Data System (BI-RADS) 3, 4 and 5 mammograms carried out in the month of October and in other months of years 2014, 2015 and 2016.

	October (2014–2016)		Other months (2014–2016)		Statistical significance
	n	%	n	%	
BI-RADS 3, 4 and 5	220	1.58	1,428	1.56	p=0.43
Other categories	13,704	98.42	90,346	98.44	
Total	13,924	100.00	91,774	100.00	

Table 2. Comparison of the proportion of Breast Imaging Reporting and Data System (BI-RADS) 3, 4 and 5 mammograms between several studies.

Classification	BI-RADS 3		BI-RADS 4		BI-RADS 5		Total	
	n	%	n	%	n	%	n	%
2013 – Rodrigues et al.[16]	761	2.44	376	1.21	33	0.11	31,196	100.00
2014 – Badan et al.[15]	605	8.35	106	1.46	11	0.15	7,249	100.00
2017 – Tomazelli et al.[14]	152,971	2.70	73,396	1.30	9,653	0.20	5,759,503	100.00
2017 – Present article	1,084	1.02	402	0.38	162	0.15	105,698	100.00

months. This fact explains the demand observed in the month of November, which is higher than other months (except October).

Although the absolute number of BI-RADS 3, 4 and 5 tests has increased in the month of October, there were no changes in the proportion of these tests in relation to the total. It was expected that women with mammary symptoms would be more affected by media campaigns and, thus, led to seek for mammograms in greater proportion, increasing the volume of BI-RADS 3, 4 and 5 mammograms. However, if this factor existed, it was not enough to significantly change the data.

It was not possible to find articles in the national literature indexed within the last five years which would describe the impact of mediatic campaigns in the search for mammographic screening. However, other national articles reported data on the classification of mammograms into BI-RADS categories (Table 2).

When compared to other studies[14-16], the present study observed a greater proportion of mammograms classified as BI-RADS 3 and 4 and a similar number of BI-RADS 5 mammograms. Some factors may be considered to explain this result. The BI-RADS classification is an international system for the evaluation of breast findings, which consider breast abnormalities estimating the risk of breast cancer. This classification does not apply solely to mammography, but also to other image tests. Little interobservational variability is expected in the evaluation of BI-RADS categories. However, it is observed that results of different centers are not the same[16]. Thus, studies that use data from several services[14,16] may be subject to greater heterogeneity than those evaluating a single center[15].

Moreover, the different socioeconomic realities found in our country may contribute so that the screening is offered in an unequal way in different locations, influencing the rate of tumor detection[10,17].

Nevertheless, the BI-RADS 5 category presented good agreement between studies. This classification offers rather typical findings with high positive predictive value[15], while categories 3 and 4 may point toward some findings of lower predictive value. This could contribute to a higher interobservational agreement in tests categorized as BI-RADS 5[18]. This reasoning also seems to be sustained for the BI-RADS classification through magnetic nuclear resonance[19,20].

Even though the study has suffered with limitations — such as the lack of histopathological confirmation for BI-RADS 3, 4 and 5 mammograms —, it offered important results. Media campaigns require high spending of public money, in addition to a mobilization by health professionals and the society. Understanding whether there really is a change in populational behavior confirms the effectiveness of these projects and may guide future decisions. Furthermore, to the authors' knowledge, this is the first Brazilian study to address Pink October in the adherence to mammographic screening. Future studies could contribute to the theme, evaluating the cost-effectiveness and the direct impact of campaigns such as this one in different social groups.

CONCLUSION

The Pink October campaign, through propaganda in the most varied media, basic health units, schools and commerce, results in a popular mobilization in the search for breast cancer screening. The increased search for mammography increases the total number of mammograms with findings which may suggest malignancy, even though it does not change the ratio of BI-RADS 3, 4 and 5 tests. This result may contribute to increase early diagnosis, allowing for the chance of improved chances of cure and decreased adoption of aggressive treatments.

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ORIGINAL ARTICLE
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ANDROGEN RECEPTOR EXPRESSION IN TRIPLE NEGATIVE BREAST CANCER AND ITS RELATIONSHIP TO PROGNOSTIC FACTORS

Expressão de receptor de androgênio em câncer de mama triplo negativo e sua relação com fatores prognósticos

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ABSTRACT

Objective: Triple negative breast cancer (TNBC) is a subset of tumors with an aggressive intrinsic biology, resulting in poor prognosis. Androgen receptor (AR) is currently one of the most studied biomarkers in TNBC, playing a role in the genesis and development of breast cancer. **Methods:** In this cross-sectional study, we retrospectively reviewed the medical records of all patients with TNBC who received care from 2012 to 2014 at a single health center in southern Brazil. Histological material from breast tumors was analyzed by immunohistochemistry for AR expression and related to age, histological grade, tumor-infiltrating lymphocytes (TILs), and Ki-67. **Results:** Of 34 TNBC cases identified, 23 (67.6%) were AR negative and 11 (32.4%) were AR positive. The average age of the patients was 51.9 years (range: 30–82 years). Among positive cases, AR was weakly expressed in 6 and strongly expressed in 5 cases. Most patients (n=28; 82.0%) had poorly differentiated tumors. Mean Ki-67 expression was 65.0% in AR-negative and 43.6% in AR-positive cases ($p<0.05$). There was a significant association between age and AR expression ($p<0.005$), which was associated with mean age 70.8 years in the strongly AR-positive group and 42.3 years in the weakly AR-positive group. The mean percentage of TILs was 38.6% in AR-positive and 39.1% in AR-negative cases ($p=0.391$). **Conclusion:** There was no significant association between AR expression and histological grade or TILs. AR positivity in TNBC was associated with older age and tumors with lower Ki-67 expression, indicating two subgroups with distinct phenotypes in patients with TNBC.

KEYWORDS: Receptors, Androgen; Immunohistochemistry; Triple Negative Breast Neoplasms.

RESUMO

Objetivo: O câncer de mama negativo triplo (triple negative breast cancer – TNBC) é um subtipo de tumores com biologia intrínseca agressiva, resultando em pior prognóstico. O receptor de andrógeno (androgen receptor – AR) é atualmente um dos biomarcadores mais estudados em TNBC, desempenhando papel na gênese e no desenvolvimento do câncer de mama. **Métodos:** Neste estudo transversal, revisamos retrospectivamente os registros médicos de todos os pacientes com TNBC que receberam atendimento de 2012 a 2014 em um único centro no sul do Brasil. O material histológico dos tumores de mama foi analisado por imuno-histoquímica para a expressão de AR e relacionado a idade, grau histológico, linfócitos infiltrantes de tumores (TILs) e Ki-67. **Resultados:** Dos 34 casos identificados de TNBC, 23 (67,6%) eram AR negativos e 11 (32,4%), AR positivos. A idade média foi de 51,9 anos (30–82 anos). Entre os casos positivos, AR foi fracamente expresso em 6 e fortemente expresso em 5 casos. A maioria dos pacientes (n=28, 82,0%) apresentou tumores pouco diferenciados. A expressão média de Ki-67 foi de 65,0% em AR-negativo e 43,6% em AR-positivo ($p<0,05$). Houve associação significativa entre a idade e a expressão de AR ($p<0,005$), associada à idade média de 70,8 anos no grupo

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com AR fortemente positivo e de 42,3 anos no grupo com AR fracamente positivo. A porcentagem média de TILs foi de 38,6% em AR-positivo e de 39,1% em AR-negativo (p=0,391). Não houve associação significativa entre expressão AR e grau histológico ou TILs. **Conclusão:** A positividade de AR em TNBC foi associada com idade mais avançada e tumores com menor expressão de Ki-67, indicando dois subgrupos com fenótipos distintos em pacientes com TNBC.

DESCRITORES: Receptores Androgênicos; Imuno-histoquímica; Câncer de Mama Triplo Negativo.

INTRODUCTION

Breast cancer is the most common malignancy among women in Brazil. Data from the Brazilian National Cancer Institute show that breast cancer accounted for 57,120 of 576,000 new cases of cancer diagnosed in 2014, being the most frequent tumor type in women (excluding non-melanoma skin cancer)[1].

Triple negative breast cancer (TNBC) is a subset of tumors characterized by lack of expression of estrogen receptor (ER) and progesterone receptor (PR), as well as an absence of amplification or overexpression of human epidermal growth factor receptor 2 (HER2)/neu gene. TNBC accounts for approximately 15 to 20% of all breast tumors and is associated with aggressive biological behavior, increased risk of recurrence, distant metastasis, and poorer survival compared with hormone receptor-positive subtypes[2-5]. A panel of molecular alterations, such as increased rate of p53 mutations, elevated Ki-67 expression, loss of function of BRCA1, and presence of several tyrosine kinase activators, has been associated with this molecular subtype of breast cancer[2].

Owing to the unfavorable biomolecular features of TNBC, conventional chemotherapy is the only treatment currently available for patients with this breast cancer subtype. Recent studies have attempted to identify biomarkers that allow us to subclassify these tumors into different prognostic groups and select patients who are candidates for more or less cytotoxic chemotherapy regimens, in addition to discovering new targeted therapies. Currently, androgen receptor (AR) is one of the most extensively studied biomarkers in TNBC[6].

AR is a protein localized in the nucleus of certain cells, where both testosterone and dihydrotestosterone bind to the AR. This receptor is normally found in the male urogenital system and in areas where hair usually grows in men. Recent studies, however, have also demonstrated its expression in breast cancer, including TNBC. According to Collins et al.[7], 77% of invasive breast carcinomas are AR positive. In addition, AR expression was commonly observed in luminal A (91%) and B (68%) tumors, but was less frequently observed in HER2/neu positive subtypes (59%). Although TNBC is defined by absence of ER and PR expression and is considered hormonally unresponsive, 35% of TNBC express AR[8]. However, the actual role of AR expression as a prognostic factor in TNBC remains unclear.

The current study was therefore designed to evaluate AR expression by means of immunohistochemistry in all TNBC cases recorded at a single health center in Southern Brazil from 2012 to 2014 and relate AR expression to prognostic factors obtained from clinical and pathological reports.

METHODS

We conducted a cross-sectional study with medical record review of breast cancer patients who received care from January 2012 to June 2014 at a single health center located in Caxias do Sul, a city in Southern Brazil. The study was approved by the Research Ethics Committee of Hospital Virvi Ramos (protocol nº. 383,616). Informed consent was waived due to the non-interventional design of the study and retrospective nature of data collection.

Data were collected from electronic medical records completed during the histopathological evaluation of biopsies and/or surgical specimens obtained at Diagnosis Laboratory of Pathology and Cytopathology. We retrospectively identified all patients with a main diagnosis of invasive carcinoma of no special type (NST), according to the 4th edition of the World Health Organization (WHO) Classification of Tumors of the Breast, published in 2012, or invasive ductal carcinoma not otherwise specified (NOS), according to the 3rd edition, published in 2003[9].

Eligible participants were all women with a diagnosis of invasive ductal carcinoma NOS or invasive carcinoma NST with triple negative phenotype (TNBC). Medical records with incomplete or missing information on clinical and pathological parameters required for analysis were excluded.

The histological material from patients with TNBC was analyzed by immunohistochemistry for AR expression and related to the following clinical and pathological parameters: patient age, histological tumor grade, tumor-infiltrating lymphocytes (TILs), and Ki-67.

IMMUNOHISTOCHEMISTRY

In all selected TNBC cases, immunohistochemical staining was performed for AR, ER, PR, HER2, and Ki-67 on 3-µm tissue sections cut from the original paraffin blocks. Sections were first deparaffinized and antigen retrieved. For each marker, immunostaining was performed on an automated immunostainer

(Autostainer Link 48; Dako Corp., Carpinteria, CA, USA) using a multiple-step staining procedure.

The following monoclonal antibodies were used: mouse anti-human AR (1:50, clone AR441, Dako); ER (1:100, clone PPG5/10, Dako); PR (1:800, clone PgR 636, Dako); and a monoclonal antibody for Ki-67 antigen (1:2000, clone MIB-1, Immunotech, Marseille, France). It was also used the polyclonal antiserum with HER2 protein for HER2/neu gene (clone SP3, Spring).

SCORING SYSTEM

Staining results were assessed independently by two pathologists. AR staining was classified using the H-score[10], which ranges from 0 to 300 and is calculated according to the following formula: (1 × percentage of cells staining weakly positive) + (2 × percentage of cells staining moderately positive) + (3 × percentage of cells staining strongly positive). H-score ≤150 was considered weak AR expression and H-score >150 was considered strong AR expression.

ER and PR were considered positive if ≥1% of tumor cells stained positive, as recommended by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP)[11].

HER2 staining was assessed using a semiquantitative score ranging from 0 to 3+, where 0 or 1+ indicate a negative, 2+ indicates an indeterminate, and 3+ indicates a positive HER2 test result (Table 1)[12]. All cases with 2+ staining underwent fluorescence *in situ* hybridization (FISH) for evaluation of HER2 gene amplification, as recommended by ASCO/CAP. The FISH assay was performed using dual red and green DNA probes corresponding to HER2 and chromosome 17 centromere (CEN17), respectively. HER2 was considered amplified when the HER2/CEN17 ratio was ≥2.2, according to ASCO/CAP guidelines[12].

For Ki-67 analyses, immunostaining was performed on an automated immunostainer (Autostainer Link 48; Dako Corp., Carpinteria, CA, USA) using a multiple-step staining procedure and a specific monoclonal antibody for Ki-67 antigen (clone MIB-1, dilution 1:2000, Immunotech, Marseille, France). The Ki-67 expression levels were expressed as the percentage of cells with positive nuclear staining among the total number of tumor cells (at least 1,000 were counted)[13]. For ki-67, a higher cutoff point (50%) was used because 70% of TNBC cases showed Ki-67 labeling indices >50%.

The percentage of TILs was assessed in paraffin-embedded tumor sections stained with hematoxylin and eosin (HE) and was defined as the percentage of lymphocytes in direct contact with tumor cells[14].

All cases were graded according to the WHO histopathological classification[15] as well-differentiated (grade 1), moderately differentiated (grade 2), or poorly differentiated (grade 3)[9].

STATISTICAL ANALYSIS

Continuous variables were expressed as standard deviation (SD) and analyzed using Student's *t*-test. Categorical variables were expressed as absolute and relative frequencies and analyzed using the χ^2 test with 95% confidence interval (95%CI). Data analysis was performed using SPSS, version 17.0. The level of significance was set at 5% ($p<0.05$).

Table 1. Relationship between androgen receptor expression and age in patients with triple negative breast cancer.

Variable	Androgen receptor expression				p-value
	Positive (n=11)		Negative (n=23)		
	n	%	n	%	
Age (years)					0.038
30–34	3	27.3	2	8.7	
35–39	-	-	5	21.7	
40–44	-	-	2	8.7	
45–49	-	-	3	13.0	
50–54	2	18.2	4	17.4	
55–59	2	18.2	1	4.3	
60–64	1	9.1	-	-	
65–69	-	-	3	13.0	
>70	3	27.3	3	13.0	
Mean±SD	55.3±18.7		50.5±13.7		NS

NS: not statistically significant; SD: standard deviation; p-values <0.05 were considered significant.

RESULTS

Among 314 patients with invasive breast carcinoma who received care at our institution from January 2012 to June 2014, 34 had TNBC (10.8%) and were included in the analysis. Of these, diagnosis was obtained for 24 patients from percutaneous biopsies and for 10 patients from surgical specimens. There were no exclusions.

The mean age of patients with TNBC was 51.9 years (SD: 15.36 years; range: 30 to 82 years). Of 34 TNBC cases identified, 23 (67.6%) were AR negative and 11 (32.4%) were AR positive. Among positive cases, AR was weakly expressed (H-score ≤150) in 6 cases and strongly expressed (H-score >150) in 5 cases. Most tumors showed high Ki-67 expression, with labeling indices above 50% in 18 of 34 cases (52.9%). A high histological grade was observed in all cases, with 28 (82.0%) tumors graded as poorly differentiated (G3) and 6 (18.0%) as moderately differentiated (G2).

The results of the relationship between AR expression and age in patients with TNBC are shown in Table 1. AR-positive patients were older (mean age: 55.3 years) than AR-negative patients (mean age: 50.5 years), but with no significant difference between groups. Specifically among AR-positive patients, 72.8% (8/11 cases) were older than 50 years (*p=0.038).*

The results of the relationship between AR expression and Ki-67, histological grade, and TILs in patients with TNBC are shown in Table 2. There was a statistically significant association between AR-positive cases and Ki-67 antigen expression <50% (*p<0.038*). In both AR-positive and AR-negative tumors, the histopathological grading was predominantly G3 (*p=0.309*). The mean percentage of TILs was 38.6% in AR-positive cases and 39.1% in AR-negative cases (*p=0.391*). There was no statistically significant association between AR expression and histological grade or TILs.

In the strongly AR-positive group (H-score >150), all patients were older than 50 years, and this variable was significantly associated with the mean age 70.8 years *(p<0.003*) (Table 3).

The mean values for Ki-67 expression, percentage of histological grade G3 and percentage of TILs, although higher in the weakly AR-positive group, did not reach statistical significance (Table 4).

DISCUSSION

In the present series, the prevalence of TNBC expressing AR was 32.3%, a rate similar to the mean rates reported in previous studies, ranging from 32 to 35%[7,8]. These data reinforce the importance of studying AR in breast cancer, since a significant number of patients with TNBC, in the near future, might benefit from new targeted therapies.

AR signaling exerts an anti-estrogenic effect, inhibiting cell proliferation in normal breast tissue, and this action is more evident in luminal breast cancer, in which the concomitant expression of estrogen receptor-α [ERα) and AR is associated with a favorable prognosis[16-18]. In contrast, AR signaling may promote cell proliferation in a subgroup of ERα-negative tumors: AR-positive breast tumors with a molecular apocrine phenotype[19-21] demonstrated synergy between AR and inhibitors of mitogen-activated protein kinase (MEK) signaling pathways. He et al. showed that AR expression is a favorable prognostic

Table 2. Relationship between androgen receptor expression and Ki-67, histological grade, and tumor-infiltrating lymphocytes in patients with triple negative breast cancer.

Variable	Androgen receptor expression				p-value
	Positive (n=11)		Negative (n=23)		
	n	%	n	%	
Ki-67					
<50%	8	72.7	8	34.8	<0.038
51–100%	3	27.3	15	65.2	
Mean±SD	43.6±22.9		65.0±20.9		<0.011
Histological tumor grade*					
G2	2	27.3	3	13.0	
G3	8	72.7	20	87.0	NS
TILs					
≤59%	6	54.5	16	69.6	NS
≥60%	5	45.5	7	30.4	
Mean±SD	38.6±32.1		39.1±26.4		NS

*G2: moderately differentiated; G3: poorly differentiated; p-values <0.05 were considered significant; TILs: tumor-infiltrating lymphocytes; NS: not statistically significant; SD: standard deviation.

factor of disease-free survival and overall survival in patients with TNBC ($p=0.032$)[22]. In addition, a recent meta-analysis including 13 studies with 2,826 patients evaluated the prognostic factor value of AR in TNBC and concluded that AR expression was associated with lower risk of disease recurrence[23].

In agreement with previous studies[6,8], the present research showed that strong AR expression is associated with older age ($p<0.05$) when AR-positive cases are subdivided into weakly and strongly positive, with a higher mean age in the strongly AR-positive subgroup (70.8 years). This association has also been reported for other molecular subtypes, for which studies have shown that AR expression was associated with older age and biologically less aggressive tumors[16-18,24,25].

Ki-67 is a nuclear protein present in proliferating cells in all phases of the cell cycle, except for the G0 (zero) phase. It is detected by monoclonal antibody MIB-1 and is currently the

Table 3. Relationship between intensity of androgen receptor expression and age in patients with triple negative breast cancer.

Variable	AR-positive cases				p-value
	H-score ≤150 (n=6)		H-score >150 (n=5)		
	n	%	n	%	
Age (years)					<0.015
30–34	3	50.0	-	-	
35–39	-	-	-	-	
40–44	-	-	-	-	
45–49	-	-	-	-	
50–54	2	33.3	-	-	
55–59	1	16.7	1	20	
60–64	-	-	1	20	
65–69	-	-	-	-	
>70	-	-	3	60	
Mean±SD	42.3±12.4		70.8±11.2		<0.003

AR: androgen receptor; SD: standard deviation; p-values <0.05 were considered significant; H-score ≤150: 1-150, weakly positive; H-score >150: 151-300, strongly positive.

Table 4. Relationship between intensity of androgen receptor expression and Ki-67, histological grade, and tumor-infiltrating lymphocytes in patients with triple negative breast cancer.

Variable	AR-positive cases				p-value
	H-score ≤150 (n=6)		H-score >150 (n=5)		
	n	%	n	%	
Ki-67					
<50%	4	66.7	4	80	NS
51–100%	2	33.3	1	20	
Mean±SD	50.0±22.8		36±23		NS
Histological tumor grade*					
G2	1	16.3	2	40	
G3	5	83.7	3	60	NS
TILs					
≤59%	3	50.0	3	60	NS
≥60%	3	50.0	2	40	
Mean±SD	42.5±34.0		34.0±32.9		NS

AR: androgen receptor; H-score ≤150: 1-150, weakly positive; H-score >150: 151-300, strongly positive; p-values <0.05 were considered significant; SD: standard deviation; *G2: moderately differentiated; G3: poorly differentiated; TILs: tumor-infiltrating lymphocytes; NS: not statistically significant.

proliferation biomarker of choice[26]. In the present study, TNBC expressing AR had lower proliferation rate than AR-negative tumors ($p<0.05$). This finding is consistent with the results of recent studies using a 30% cutoff point[6] or mean Ki-67 values[24]. In our study, significance was found in the two methods of analysis; however, a higher cutoff point (50%) was used because 70% of TNBC cases showed Ki-67 labeling indices >50%.

The evaluation of histological grade showed no association with AR expression, a finding consistent with previous reports[6,24]. The attempt to subclassify AR expression into strong and weak showed no statistical significance in relation to Ki-67 or histological grade, and a possible explanation for this may be the extremely small number of patients with TNBC expressing AR positivity (n=11).

Evidence suggests that the immune system plays a role in breast cancer and that the presence of TILs is a prognostic factor in this setting[27]. In the present study, however, there was no statistical relationship between AR expression or intensity of AR expression and TILs.

Recently, Pietri et al. demonstrated an overview of AR signaling pathways in different breast cancer subtypes, providing evidence that its oncogenic role is likely to be different in distinct biological and clinical scenarios, including TNBC[28]. Considering that the main treatment of TNBC[29] is chemotherapy, *in vitro* studies show that AR activation can reduce chemotherapy efficacy in LAR subtype through the AR-mediated transcriptional regulation of pro- and anti-apoptotic genes, suggesting the usefulness of an AR block combined with chemotherapy in this setting[30].

The present study has some limitations that should be noted. The small sample size and the retrospective nature of medical record review limit the ability to reliably generalize the findings. Despite the advantages of assessing Ki-67, histological grade, and TILs, the evaluation of these parameters reflects an analysis of small tumor areas, through biopsies and surgical specimens, and not of the whole tumor, which can be a limitation due to tumor heterogeneity, combining more or less proliferative areas with various degrees of histological differentiation[31]. Another potential bias is that we analyzed material from both breast biopsies and surgical specimens. However, the sole analysis of surgical specimens would not be feasible, since many patients with TNBC present at initial diagnosis with distant metastases, which precludes curative surgery. Moreover, many patients with TNBC initiate treatment with neoadjuvant chemotherapy (before surgery), preventing the analysis of important pathological parameters, such as histological grade, Ki-67, tumor size, and number of affected axillary lymph nodes. This fact was observed in the present study, since a significant number of patients with TNBC showed complete pathological response to neoadjuvant chemotherapy, i.e., complete tumor remission.

CONCLUSION

This study showed distinct subgroups of patients with TNBC when tumor expression of AR was observed. Strong AR expression in patients with TNBC was associated with older age and tumors with low proliferation rate, as demonstrated by Ki-67 assessment, and probably less aggressive behavior from a biological point of view. The identification of subgroups of AR tumor expression in patients with TNBC may be useful in guiding health professionals into a more individualized approach and developing specific therapeutic strategies, in addition to improving monitoring and surveillance. Furthermore, it is known that drugs that bind to AR are hormone therapy drugs with a low incidence of side effects and excellent tolerability, which makes this horizon even more promising considering not only drug efficacy but also treatment effectiveness in AR-positive TNBC patients. Nevertheless, further prospective studies investigating AR expression in a larger number of patients with breast cancer are required to better understand the molecular mechanisms involving AR, which is critical for the development of new therapeutic strategies in breast cancer.

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ORIGINAL ARTICLE
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THE VALIDITY OF AN ADJUSTABLE COMPRESSION VELCRO WRAP FOR THE TREATMENT OF PATIENTS WITH UPPER LIMB LYMPHEDEMA SECONDARY TO BREAST CANCER: A PILOT STUDY

Validação de uma vestimenta de contenção para tratamento de linfedema de membro superior secundário ao câncer de mama: estudo piloto

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ABSTRACT

Objective: To analyze the efficacy of an adjustable compression Velcro wraps used to reduce limb volume as a form of treatment for upper limb lymphedema secondary to breast cancer. **Methods**: Women with lymphedema who had already undergone conventional treatment with compression bandaging were included. These patients were recruited through an evaluation in which the manual perimetry was applied using the truncated cone formula, and in which lymphedema were considered as a difference greater than 10% and/or 200 mL between the limbs. Patients wore their compression devices daily, taking them off only for a shower. In a period of one month of use, manual lymphatic drainage was not applied. Performing exercises was allowed 3 times a day. Patients returned after one month to have their limb volume reassessed and also to respond to a questionnaire. **Results**: A total of 9 patients were evaluated, and the median volume difference between the affected limb and the control during the first evaluation was 564.4 (SD=443.2) mL. At the reevaluation, the median difference was 390.6 (SD=306.8) mL. There was a significant difference when comparing the volumes at the evaluation and reevaluation (p=0.008). The degree of satisfaction was 9 (SD=1.3). **Conclusion**: The adjustable compression Velcro wrap was effective in the reduction of limb volume in with lymphedema. In addition, the patients reported that the device was more practical and more comfortable compared to the compression bandage. Patients who live in other cities or who are not available to perform daily treatment can benefit from the use of the device.

KEYWORDS: Physiotherapy; lymphedema; breast cancer.

RESUMO

Objetivo: Analisar a eficácia de uma vestimenta de contenção em velcro para redução do volume do membro como forma de tratamento de linfedema de membro superior secundário ao esvaziamento axilar por câncer de mama. **Métodos**: Foram incluídas mulheres com linfedema que já tivessem realizado o tratamento convencional com enfaixamento compressivo. O recrutamento dessas pacientes foi através da avaliação com a perimetria manual aplicada na fórmula do cone truncado,

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considerando linfedema uma diferença maior que 10% e/ou 200 mL entre os membros. As pacientes deveriam utilizar diariamente a vestimenta, só retirando para tomar banho. Nesse período de um mês de uso, não deveriam fazer drenagem linfática manual, e sim apenas exercícios linfomiocinéticos três vezes ao dia. As pacientes retornaram após um mês para a reavaliação do volume do membro e também responderam a um questionário. **Resultados**: Foram avaliadas 9 pacientes, sendo que a mediana de diferença de volume entre o membro afetado e o controle na primeira avaliação foi de 564,4 (DP=443,2) mL. Na reavaliação, a mediana da diferença foi de 390,6 (DP=306,8) mL. Houve diferença significativa quando comparados os volumes na avaliação e na reavaliação (p=0,008). O grau de satisfação da vestimenta foi de 9 (DP=1,3). **Conclusão**: A vestimenta mostrou-se eficaz como alternativa na redução do volume do membro com linfedema, e os pacientes relataram ser mais prática e proporcionar maior comodidade quanto comparada ao enfaixamento compressivo. Pacientes que moram em outras cidades ou que não têm disponibilidade para realizar tratamento diariamente podem se beneficiar do uso da vestimenta.

PALAVRAS-CHAVE: Fisioterapia; linfedema; câncer de mama.

INTRODUCTION

Lymphedema is a potential side effect of oncologic treatment followed by lymph node dissection. It is a chronic, progressive and debilitating pathology and is characterized by the collection of fluid in the interstitial tissues. According to a meta-analysis study, its incidence in cancer survivors is 15%.[1]

Estimates of the incidence and prevalence of lymphedema related to breast cancer vary considerably in the literature. Factors responsible for this variation include lack of standardized diagnostic criteria, measurement procedures, methodological limitations of studies, variations in populations and postoperative follow-up periods. In general, the prevalence of lymphedema varies between 9% and 40%, affecting 24–49% of women after mastectomy, 4–28% after lumpectomy with axillary dissection and 5–34% after surgery and radiotherapy. Breast cancer statistics in Brazil reveal that about 3–5 thousand patients with breast cancer will develop lymphedema.[2]

Regarding conservative treatments, complex decongestant physical therapy (CDPT) has been highlighted as the best way to reduce the volume of upper limb lymphedema. The therapy is divided into two phases. The first phase aims at the maximum reduction of limb volume through skin care, manual lymphatic drainage (MLD), physical exercises and inelastic compression bandages. The maintenance phase, or second phase, comes immediately afterwards. It consists of the adaptation of elastic compression stockings, exercises and self-massage, in order to preserve and optimize the results obtained in the initial phase.[3]

Inelastic compression bandaging is one of the main factors responsible for reducing limb volume, but it needs to be performed daily or every other day for the pressure to be within the expected range. However, patients with limb bandages have difficulties bathing and performing activities of daily living. It is believed that by replacing the bandage with an easy-to-wear wrap with ideal compression, the patient's life would be made easier. In the world literature, there is little information on the use of alternative devices for compressive bandaging for the treatment of lymphedema. Patients who live far from health centers or who lack the time needed to undergo daily physical therapy treatment can benefit from the use of the compression wrap, since it is much faster and more practical than conventional compression bandaging. Therapies that use simple application methods, such as compression wraps, are extremely valuable, due to the chronicity of lymphedema. The wrap is a simple solution that seeks to reduce costs, treatment time, and the number of doctor visits, which facilitates self-care and provides greater patient independence.[4]

The objective of this study was to analyze the validity and efficacy of an inelastic Velcro wrap for the treatment of upper limb lymphedema in patients with lymphedema secondary to breast cancer. The limb was assessed by manual perimetry and the volume was calculated in milliliters (mL) using the truncated cone formula. We sought to describe the benefits or harms related to the use of adjustable compression Velcro wraps as a substitute for the traditional compression bandaging.

METHODS

We performed a prospective, descriptive cross-sectional study. Patients were selected for convenience. This study was approved by the Ethics Committee, and each patient signed an informed consent form. Patients were also requested to sign an authorization for image, interview and questionnaire use.

We included women with upper limb lymphedema who underwent axillary lymph node dissection for the treatment

of breast cancer and who had already undergone conventional CDPT treatment with compressive bandaging.

Patients with primary or bilateral lymphedema and with perimetry within the normality value (less than 10% and/or 200 mL of difference in volume between affected and control limbs) were excluded, as well as individuals with a postoperative period of less than six months.

Lymphedema was assessed by manual perimetry before and after the compression wrap. A physical examination by palpation was performed to verify the presence of fibrosis and a Godet sign. Oncology clinical data were obtained from the available medical records at the institution.

Perimetry was performed with a flexible tape measure, starting from the intra-articular line of the elbow, measured superiorly and inferiorly every 7 cm (7, 14 and 21 cm). The evaluation was performed bilaterally for the comparison of the affected limb with the unaffected limb (control), during which the patient should be naked, seated, and with limbs relaxed and supported on a table. Measurements of the manual perimetry were applied in the truncated cone Equation 1 to obtain the limb volume:

$$V = \frac{h\,(C1^2 + C1 \times C2 + C2^2)}{12\,\pi} \quad (1)$$

In which:
V=final volume of the limb segment;
C1 and C2 = circumferences between the measured points;
h=distance between the circumferences (C1 and C2 in each segment), all calculated in centimeters.

A volume difference greater than 10% and/or 200 ml between the upper limbs was considered lymphedema. The degree of upper-limb lymphedema was classified according to Stillwell et al. (1969), quoted by Vries et al.[4], into: 0.0-10.0% insignificant; 10.1-20.0% slight; 20.1-40.0% moderate; 40.1-80.0% marked and >80.1% severe.

In the first appointment, patients received a questionnaire asking socio-demographic information and a form with instructions on how to use the compression wrap. Patients also received a diary to keep daily and weekly records of complaints and sensations perceived, as well as the amount of time of daily use (day and night). Patients were then instructed to wear the wrap most of the time — including at bedtime — and should only remove it when bathing or to wash it. They were also instructed to adjust the wrap every time they felt it becoming loose, and to check it every two hours.

The self-adjusting Velcro compression wrap is made of a type of rubber whose base composition is polychloropene, a synthetic elastomeric polymer of chloropene. On one side the rubber is coated with polyamide and, on the other, it is coated with 100% polyester plush. The correct way to wear the glove accompanying the compression wrap is shown in Figure 1.

Patients were advised not to undergo MLD during the time they were wearing the wrap, but were instructed to do exercises three times a day to improve lymphatic system function. Exercises included finger flexion and extension, hand flexion and extension, radial and ulnar deviation, wrist flexion and extension, elbow flexion and extension, pronation and supination of the hand, shoulder rotation, pulley, finger ladder and skin care. Patients received printed guidelines for the exercises.

After a month, they returned to have their limb volume reassessed through manual perimetry and they also answered a questionnaire containing information such as degree of satisfaction with the compression wrap in relation to traditional dressings, time of use, pros and cons, etc.

The study population was characterized by descriptive statistics (mean, median, standard deviation, maximum and minimum values and percentage). Adherence to normality was verified using Kolmogorov-Smirnoy and Shapiro-Wilk tests. We assumed a significance level of 5% for all statistical tests. Statistical analysis of limb volume differences before and after the use of the wrap was performed through univariate analysis using the Wilcoxon test. Statistical analyses were performed using SPSS 20.0 for Windows.

RESULTS

Ten women with upper limb lymphedema resulting from axillary lymph node dissection as a treatment for breast cancer participated in the study. However, the sample was composed of

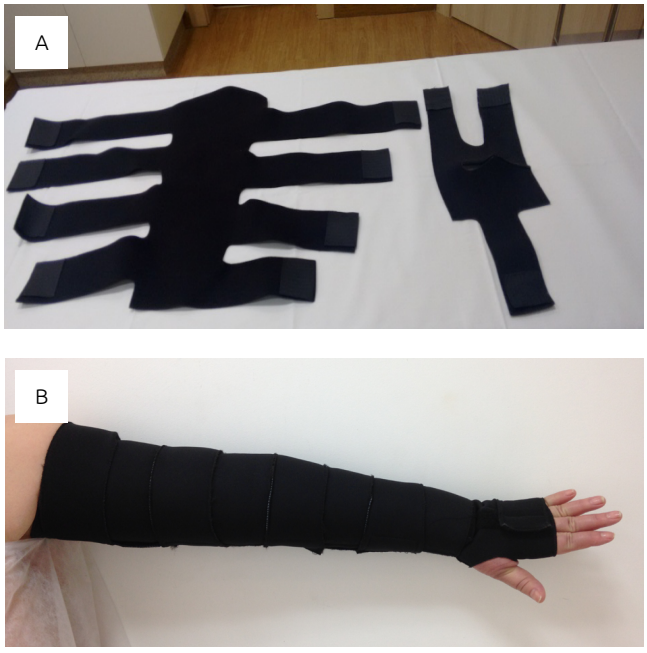


Figure 1. (A) Self-adjustable compression (Velcro) wrap for upper limb volume reduction in lymphedema; (B) instructions on how to use glove and compression wrap for the treatment of upper limb lymphedema.

nine patients since one of them used the compression wrap for only one day and refused to continue the treatment, claiming that she had difficulty putting on the device by herself. The mean age of the 9 participants was 58.6 years (SD=11.6), with a minimum age of 41 and a maximum age of 82. The mean body mass index (BMI) was 30.8 (SD=5.1), ranging from 22.0–39.5.

Regarding cancer staging, 44.4% (n=4) were stage II and 55.6% (n=5), stage III. All patients underwent axillary lymph node dissection and modified radical mastectomy, in addition to chemotherapy. Only one patient (11.1%) was treated with neoadjuvant chemotherapy. The other patients were treated with adjuvant therapy. However, 77.8% (n=7) underwent radiotherapy and 44.4% (n=4) underwent hormone therapy — tamoxifen (66.7%) and anastrosole (22.2%).

Eight patients were white (88.9%) and one was black, 55.6% were married, 33.3% were divorced and 11.1% were single. Regarding education, 22.2% (n=2) had a postgraduate diploma, 22.2% (n=2) had an undergraduate diploma, 22.2% (n=2) had incomplete higher education, 22.2% (n=2) had incomplete secondary education and 11.1% (n=1) had complete secondary education. We observed that patients with a lower level of education had more difficulty answering the questions on the daily and weekly questionnaires.

All patients were right-handed and lymphedema was more common on the left side (55.6%, n=5). The mean postoperative time was 93.4 months (SD=28.1) and the mean time interval between surgery and the onset of lymphedema was 27.5 months (SD 14.0). Numerical variables are shown in Table 1.

The median volume difference between the affected limb and the control at the first assessment was 564.4 mL (SD=443.2). In the last measurement, the median difference was 390.6 mL (SD 306.8). We observed a statistically significant difference when comparing the volumes in the first and last measurements ($p = 0.008$) (Table 2).

Decreased limb volume meant that the degree of lymphedema was also modified. Most of the patients underwent stage reduction. Initially, 55.6% of the patients had mild lymphedema (n=5), 22.2% had moderate lymphedema (n=2) and 22.2% had marked lymphedema (n=2). After the intervention, 33.3% of the patients were below 10% (n=3) — that is, within the normal range —, 44.4% presented mild lymphedema (n=4) and 22.2%, moderate.

Figure 2 shows the beginning and end of treatment in one of the patients, in which marked lymphedema was reduced to moderate. The right upper limb had a volume of 3645.6 mL, compared to 2807.8 mL after the application of the compression wrap.

The most frequent complication in the postoperative period was seroma, which occurred in 44.4% of the cases (n=4), followed by cicatricial dehiscence and infection, both in 11.1% of the patients (n=1). The 7 patients who underwent radiation therapy (77.7%) had radiodermatitis in 28.6% of the cases (n=2). Erysipelas occurred in 22.2% of cases (n=2).

The main treatments previously given to the patients included MLD, compression bandaging, skin care, exercises and use of elastic sleeves in all cases. Also, 44.4% of patients used kinesio taping. None of the patients used laser or pneumatic compression.

Table 1. Numerical variables of patients with upper limb lymphedema.

Numerical variables	Mean	Median	SD	Minimum	Maximum
Age	58.56	57.00	11.62	41.00	82.00
BMI	29.69	30.80	5.15	22.00	39.50
Surgery time (months)	93.44	75.00	42.38	55.00	162.00
Lymphedema time (months)	65.89	51.00	44.39	6.00	130.00
Time between surgery and lymphedema onset (months)	27.56	24.00	14.0	13.00	49.00
Number of positive lymph nodes	2.78	3.00	2.82	0.00	8.00
Number of dissected lymph nodes	18.33	16.00	5.74	13.00	32.00
Wrap time use per day (hours)	19.40	21.00	4.05	14.00	23.00

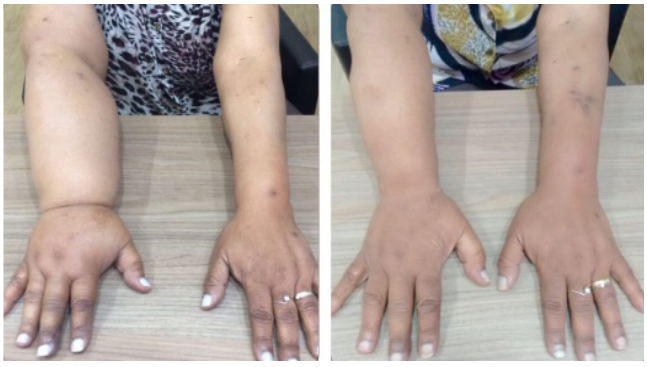
BMI: body mass index; SD: standard deviation.

Table 2. Volume difference between affected limb and control limb before and after the compression wrap in patients with upper limb lymphedema.

Numerical variables	Mean	Median	SD	Minimum	Maximum	P-value*
Volume difference before (mL)	643.48	564.40	443.16	214.00	1587.90	0.008
Volume difference after (mL)	375.93	390.60	306.79	29.30	865.60	
Volume difference before (%)	21.67	18.60	12.34	10.30	43.60	0.008
Volume difference after (%)	13.38	13.10	10.76	1.20	30.20	

SD: standard deviation *Wilcoxon test

Fibrosis remained both before and after the use of the compression wrap, that is, the containment device did not promote fibrosis improvement nor did it reduce the Godet sign. However, the use of the wrap importantly impacted the sensation of heaviness and limb volume increase, as shown in Table 3. Before wearing the wrap, 88.9% of the patients reported experiencing a sensation of heaviness, which was reduced to 11.1% after use. All patients reported reduced limb volume and 88.9% felt more protected when wearing the compression wrap. Patients complained that the Velcro got loosened and grabbed onto their clothes. They also reported that their arms sweated a lot during the exercises, and it was necessary to reset the device every two or three hours, because it would slip and get loose.



Day 0 Day 30

Figure 2. Initial assessment (day 0) prior to treatment; Reassessment (day 30) after the use of the Velcro wrap. A reduction from marked to moderate lymphedema can be observed.

Table 3. Evaluation of the complaints, sensations and possible complications perceived by patients during the period of use of the compression wrap

Complaints, sensations and complications during the use of the compression wrap	n	%
Fibrosis before	3	33.3
Fibrosis after	3	33.3
Godet sign before	3	33.3
Godet sign after	3	33.3
Sensation of heaviness before	8	88.9
Sensation of heaviness after	1	11.1
Volume increase before	9	100
Volume increase after	5	55.6
Arm discomfort	5	55.6
Arm tightening	4	44.4
Stopped going out because of the wrap	2	22.2
Felt protected wearing the wrap	8	88.9
Felt insecure wearing the wrap	2	22.2
Reported difficulty wearing the wrap	5	55.6
Limb weight decreased	8	88.9
Limb size decreased	9	100
Wrap came off	9	100

The mean patient satisfaction level was 9 (SD 1.3), on a scale ranging from 0-10, with 7 being the minimum value and 10 being the maximum value attributed by the patient. All patients evaluated the wrap as a better option in relation to conventional compression bandages in that it was more practical and convenient.

DISCUSSION

Although the literature shows a consensus about compression bandaging as a crucial part of lymphedema treatment, patients have difficulty self-bandaging their arms, especially those who lack access to physiotherapy with the necessary frequency. The purpose of the compression wrap is to enable these patients to correctly use the device as an auxiliary form to treat lymphedema with satisfactory results.

This pilot study sought to analyze the benefits and possible harms caused by compression wraps. After one month, the Velcro and the tissue were slightly damaged due to constant use, and patients expressed discomfort about the heat. New materials should be looked into for more durable and fresher wraps.

Late-onset lymphedema is more difficult to treat than initial lymphedema. Although the patients had lymphedema for an average of 5 years, we observed a significant limb volume reduction.

In a study of 1,054 women with breast cancer undergoing axillary lymph node dissection, the incidence of lymphedema was 17% at 2 years postoperatively, and 30% at 5 years.[6] The mean rate of appearance of lymphedema in the present sample was 2 years, and the later case was 4 years postoperatively.

Oremus et al. systematically reviewed secondary lymphedema cases and observed that most authors considered lymphedemas after more than 6 months postoperatively.[7] When analyzing the diagnostic of lymphedema, most of the studies considered differences between homolateral and contralateral limbs above 10% and/or 200 mL, as was proposed in the present study.

Since lymphedema is a chronic lymphatic disorder, patients require prolonged physiotherapeutic follow-up. Patients often take part in the first phase of the CDPT, but they end up neglecting the second phase, in which limb volume can increase again. The patients studied had previously undergone a CDPT and, although they were in the maintenance phase, they had significant increase in limb volume (more than 10% or 200 mL of difference compared to the contralateral arm).

Vignes et al. conducted a study of 682 patients with lymphedema to check limb volume control during the maintenance phase, observing a better response in subjects who used daytime elastic and inelastic compression bandages at bedtime.[8] Therefore, we suggest that the Velcro wrap proposed in our study may also be used as a form of nocturnal inelastic compression

bandaging, contributing to both edema reduction and maintenance phases.

All patients should have previously received compression therapy to enable a comparison with the wrap. However, a study showed that the most used technique in the treatment of upper and lower limb lymphedema was isolated MLD and that bandaging was performed in only 18% of cases.[9] In the present sample, MLD was not performed, demonstrating that this technique is not the most important in limb volume reduction, but rather the combination of inelastic compression with exercises.

A pilot study published in 2016 sought to record the performance of a compression wrap in 17 patients with lymphedema or venous ulcers who used a contention device as a self-care option in the treatment and maintenance of lower limb edema. Patients with lymphedema were also treated with MLD and received guidelines regarding skin care. They observed a reduction in limb circumference, demonstrating that the adjustable Velcro compression wrap may provide a simple, clinically effective and patient-acceptable solution for self-care with compression.[4]

Another analysis was performed in 30 individuals with moderate to severe lower-limb lymphedema, divided into two groups: one wearing compression wraps and another wearing multilayer inelastic compression bandages. It was observed that the wrap was associated with greater reduction in limb volume after 24 hours compared with compression bandaging. As in the methodology proposed here, patients were able to self-apply the device after receiving instructions on how to use it and set the correct compression rate every 2 hours.[10]

Mosti et al. compared the efficacy and comfort of compression wraps and compression bandaging and they found that wrap devices are effective and well tolerated not only during maintenance therapy, but also in the initial decongestant treatment phase of patients with lower limb venous edema.[11]

A literature review of the use of compression wraps has shown that most studies investigated lower limb lymphedema. There is little scientific evidence for the use of adjustable compression devices in patients with lymphedema, considering that most of the evidence is in the form of descriptive works, case studies or relatively small research studies. These studies are performed over a short period of time and do not reflect the long-term nature of these chronic conditions and their treatment. However, there is clinical evidence that compression wrap devices improve the quality of life and independence of patients.[12]

Although infection is a significant risk factor for lymphedema,[13] patients in this study reported low rates of postoperative infection and erysipelas, probably due to the small sample size. Radiation therapy is also a risk factor, as it promotes the formation of tissue fibrosis, with consequent lymphatic vasoconstriction, significant damage to the lymph node filtration function and altered immune response. Lymphatic anastomoses are still impaired by cicatricial fibrosis.[14] We observed that more than half of the patients required radiotherapy as a complementary treatment.

It is common patients have symptoms such as a sensation of heaviness, pain and discomfort, which significantly reduces their physical function, mobility and ability to perform daily activities, consequently worsening their quality of life. Psychological and emotional concerns are also present. Patients commonly report increased levels of distress and a feeling of helplessness, a fear of a possible disease progression and adverse changes in body image and self-esteem.[15,16] A sensation of heaviness occurred in 88.9% of the patients before the compression wrap. However, after its use, only 11.1% of these patients mentioned the discomfort. Campanholi et al.[17] observed good agreement between manual perimetry and subjective evaluation through self-report of heaviness and/or upper limb swelling. When limb perimetry decreases, sensation of heaviness is reduced.

Interstitial plasma protein accumulation and insufficient proteolytic activity promote angiogenesis with neovascularization and fibrosis, impeding lymphedema regression.[18] Fibroses intensify lymphatic system lesions, damaging the flow of interstitial fluid and avoiding lymphatic reabsorption.[19] Compression wraps showed no interference with fibrosis, since the patients who had fibrosis, continued to have it even after the use of the compression device. We emphasize the necessity to wear the compression wrap in association with physiotherapeutic treatment that treats the fibrosis through specific manual therapy, in order to provide a greater decrease in the limb volume.

Just as Ehmann et al. cite that more studies with the contention device should be done, we believe that there is a need for studies mainly for upper limb lymphedema, since most of those found in the literature focused only on lower limbs.[5]

CONCLUSION

Adjustable compression Velcro wrap is an interesting method for upper limb volume reduction in patients with lymphedema, since there was a significant limb volume difference before and after the use of the device.

We believe that compression wraps can be considered an alternative method for reducing limb volume in patients with lymphedema. Based on patients' comments, they considered the compression wrap was better, more practical and more comfortable when compared to compression bandaging.

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FREQUENCY AND FACTORS ASSOCIATED WITH INJURY TO THE AXILLARY VEIN IN WOMEN THAT UNDERWENT AXILLARY LYMPHADENECTOMY DURING BREAST CANCER SURGICAL TREATMENT

Frequência e fatores associados à lesão da veia axilar em mulheres submetidas à linfadenectomia axilar no tratamento cirúrgico do câncer de mama

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ABSTRACT

Objective: To evaluate which variables are considered risk factors associated with injury to the axillary vein during lymphadenectomy in the surgical treatment of breast cancer patients. **Methods:** Retrospective study performed through the electronic record analysis of 1,007 patients who underwent axillary lymph node dissection at Hospital Erasto Gaertner, from January 2010 to December 2014. We assessed the following risk factors using a standard questionnaire: age, body mass index (BMI), presence of palpable axillary metastasis in the clinical examination, sentinel lymph node pre-lymphadenectomy, presence of axillary metastasis in the perioperative period, size of metastasis and if it was adhered to axillary vessels, presence of pectoralis muscle invasion, resection of the pectoralis minor muscle, axillary incision separated from breast incision, prior radiotherapy, neoadjuvant chemotherapy, and pre and postoperative staging. For each patient who presented injury to the axillary vein, we paired them with two homogeneous controls (age, BMI, preoperative staging, surgical proposal, and neoadjuvant treatment). **Results:** Thirteen patients had injury to the axillary vein. In the perioperative evaluation, in most of them, the axilla was positive in the injury group (10 cases = 76.9%) and control group (12 cases = 46.1%), and it was adhered to axillary vessels in 10 cases in the injury group (76.9%) and 7 in the control group (26.9%). **Conclusion:** In this study, the presence of axillary metastasis in the perioperative evaluation, as well as that adhered to the axillary vessels, is associated with an increased risk of injury to the axillary vein during lymphadenectomy.

KEYWORDS: Breast neoplasms; Surgery; Treatment; Lymphadenectomy; Axillary vein.

RESUMO

Objetivo: Avaliar quais variáveis se apresentam como fatores de risco associados à lesão da veia axilar durante a linfadenectomia no tratamento cirúrgico de pacientes portadoras de câncer de mama. **Métodos:** Estudo retrospectivo realizado por meio da análise de prontuário eletrônico de 1.007 pacientes submetidas a esvaziamento axilar no Hospital Erasto Gaertner, no período de janeiro de 2010 a dezembro de 2014. Foram avaliados, por meio de um questionário padrão, os seguintes possíveis fatores de risco: idade, índice de massa corpórea (IMC), presença de metástase axilar palpável no exame clínico, linfonodo sentinela pré-linfadenectomia, presença de metástase axilar no transoperatório, tamanho da metástase e se estava aderida aos vasos axilares, presença de invasão do músculo peitoral, ressecção do músculo peitoral menor, incisão axilar separada da incisão mamária, radioterapia prévia, quimioterapia neoadjuvante e estadiamento pré e pós-operatório. Para cada paciente que apresentou lesão de veia axilar foi realizado pareamento com dois controles homogêneos (idade, IMC, estadiamento pré-operatório, proposta cirúrgica e tratamento neoadjuvante). **Resultados:** Treze pacientes apresentaram lesão da veia axilar. Na avaliação transoperatória, em sua grande maioria,

Study carried out at Hospital Erasto Gaertner – Curitiba (PR), Brazil.
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a axila estava positiva no grupo da lesão (10 casos = 76,9%) e no grupo controle (12 casos = 46,1%) e encontrava-se aderida aos vasos axilares em 10 casos no grupo da lesão (76,9%) e em 7 (26,9%) no grupo controle. **Conclusões:** Neste estudo, a presença de metástase axilar na avaliação transoperatória, bem como aderida aos vasos axilares, está associada ao risco aumentado de lesão de veia axilar durante a linfadenectomia.

DESCRITORES: Neoplasias da mama; Cirurgia; Tratamento; Linfadenectomia; Veia axilar

INTRODUCTION

Breast cancer is more prevalent among females and represented 25.2% of all types of breast neoplasms diagnosed in women in 2015, with about 1.67 million new cases. It is the second cause of cancer death after lung cancer in developed countries, and it is the main reason of death by the disease in developing countries with a total of 521,900 cases in general[1].

Although the axillary lymphadenectomy is controversial in specific situations, it remains part of the surgical treatment in patients with invasive breast cancer and metastases in the axillary lymph nodes[2]. More specifically, this treatment is applicable to ill patients with N1 or N2 tumors, according to the TNM system[3].

However, despite the regular public policies developed in the area and programs of mammographic tracking widely recommended for asymptomatic women with early diagnosis strategy — besides contributing to the decrease of the cancer presentation stage, also known as down-staging —, about a third of female patients in the United States suffer tumors with regional metastases (axillary lymph nodes) at the moment of diagnosis[4,5].

In Brazil, according to statistics from the Brazilian Department of Health (2012), only 18% of these cancers are limited to breast in the diagnosis (pathological staging), even though efforts are done to provide mammographic coverage for all women older than 40 years[6]. This means that, in proportion, more patients undergo the axillary approach in Brazil than in the United States.

The conventional axillary lymphadenectomy involves resection of lymph nodes at levels I and II, as Berg[7] describes. These dissections have therapeutic roles and enable staging the disease, as well as evaluating prognosis[8]. Unfortunately, the axillary approach is responsible for several functional sequelae due to surgical treatment, including lymphedema, paresthesia, restriction of the movement amplitude and pain in the arm ipsi laterally to dissection of lymph nodes. Although unsatisfying cosmetic results due to the approach of breast tumors may be minimized through oncoplastic surgery or through methods such as reconstruction with implants and with myocutaneous flaps, we may not do many things to repair functional sequelae[9].

Paresthesia referred by patients is associated with the section of the intercostobrachial nerve that crosses the axilla during the lymphadenectomy. Nevertheless, this is the smallest complication and it is not a reason of complaints about limitation of quality of life in the majority of cases[10].

Lymphedema is by far the most severe intercurrence of complex clinical management with higher impact on the patient's quality of life. Studies show that the incidence rates of complications and sequelae in the arm, including lymphedema, are directly associated with radicality of the locoregional treatment[11,12].

This complication that appears in 6 to 50% of the patients is associated with several risk factors: extensive surgery, number of removed lymph nodes, injury to the vessels and nerves present in the axillary content and axilla-adjuvant radiotherapy[13-15].

Injury or thrombosis to the axillary vein and irreversible injury to motor nerves are very rare complications throughout the axillary lymph node dissection.

This paper aimed to determine which variables are present as risk factors associated with injury to the axillary vein during the lymphadenectomy, in the surgical treatment of a female breast cancer patient.

METHODS

We performed a retrospective study through analysis of electronic medical records from 1,007 patients who underwent axillary lymphadenectomy during the surgical treatment of breast cancer at Hospital Erasto Gaertner from January 2010 to December 2014. We evaluated the following possible risk factors of injury to the axillary vein: age, body mass index (BMI), presence of axillary metastasis palpable at preoperative period, size of axillary metastases in the perioperative period, sentinel lymph node pre-lymphadenectomy, presence of axillary metastasis adhered to axillary vessels, preservation or section of pectoralis minor muscle, axillary incision separated from breast incision, prior radiotherapy, neoadjuvant chemotherapy, and pre and postoperative staging (Appendix 1). We created two "cases and controls" samples of the same source, with the same population. Each patient that presented injury to the axillary vein was paired with two control cases, which were then compared regarding the following factors: age, BMI, preoperative staging, and proposed treatment (surgery or neoadjuvant chemotherapy).

Data were grouped in contingence tables by variable to make the statistical analysis process easier. The chi-square non-parametric test evaluated the existence of a significant difference between the levels of explanatory variables due to the answer variable.

We used another mathematical model as well. We adopted the logistic regression analysis for the statistical technique, whose main purpose is providing a mathematical equation (formula)

that allows the investigator to replace the "X" values (studied variables) and whose result portrays their association with the outcome (in this case, injury to the axillary vein).

This model is generated through a robust sampling. Since this study had a small representative subgroup (39 patients – 13 in the injury group and 26 in the control), we used a process for generating new samples called bootstrap, which creates new observations based on the initial records through a randomized sampling with replacement. Thus, we created 10,000 observations for patients with injury and value equal to 1 and another 10,000 for patients without injury (control) and value equal to 0, with a total sample of 20,000 observations, as presented in Figure 1.

The Research Ethics Committee from *Liga Paranaense de Combate ao Câncer* approved the paper in August 2016.

RESULTS

We found 13 patients with injury to the axillary vein during the lymphadenectomy among the 1,007 electronic records evaluated, of whom 10 had an isolated vein injury, 2 had a vein injury associated with thoracodorsal pedicle injury and 1 had injury to the vein and long thoracic nerve. Each patient with an injury was paired with two controls, resulting in a total sample of 39 patients.

The average age of participants was 56.6 years old in the injury group and 56.7 in the control group, which varied between 40 and 82 with predominance of the fourth and fifth decades (46 and 23%, respectively).

The average BMI found was 26.5 kg/m^2 in the injury group and 26.1 kg/m^2 in the control group, that varied from 18 to 40 kg/m^2; 61% of the patients were below 30 kg/m^2 and 23% were above this range.

We observed 9 cases of palpable axillary metastasis (69.2%) during clinical examination in the group with axillary vein injury compared with 14 (53.8%) in the control group. The Ec III-IV (27 cases = 69.2%) and Ec I-II (12 cases = 30.7%) cases were more prevalent.

We performed the modified mastectomy according to Patey in 30 cases (76.9%), the quadrantectomy and axillary lymphadenectomy in 8 cases (15.3%), and 1 patient (7.6%) underwent chest wall resection.

Only 6 (15.3%) patients performed a biopsy of the sentinel lymph node before axillary lymph node dissection.

$$Injury = 1/((1+\exp(-(-54.17185+2.81483*Meta\_Pre\_OP-23.58244*BLNS+68.80405*Meta\_Trans\_OP+24.68458*Meta\_Ava+0.44370*TM-2.24539*Imp+25.38924*RMPM+29.04267*RXT+3.05412*QT-70.24175*EST\_POS\_IIIB+29.09904*EST\_POS\_IIA-66.62745*EST\_POS\_IIIA-65.94936*EST\_POS\_IIIC)))$$

Figure 1. Mathematical model

Most of the axillae was positive in the perioperative assessment, in the injury group (10 cases = 76.9%) and control group (12 cases = 46.1%), and was adhered to axillary vessels in 10 cases (76.9%) in the injury group and in 7 (26.9%) in the control group.

This study showed that the lymph nodes were divided into size according to the largest diameter. We observed that lymph nodes measuring 1-3 cm were more prevalent (8 cases = 61.5% in the injury group compared with 5 cases = 19.2% in the control group), whereas those larger than 3.1 cm were observed in 3 cases in the injury group (23.0%) and 4 in the control group (15.3%).

In 6 (46.1%) and 5 (19.2%) cases in the injury and control group, respectively, we found invasion of the pectoralis muscle through axillary metastasis.

We observed resection of the pectoralis minor muscle during the axillary lymphadenectomy in 13 cases in the injury group (100.0%) and 24 in the control group (92.3%). The control group (11 cases = 42.3%) used more the axillary incision separated from the breast incision than the injury group (5 cases = 38.0%).

Only 1 patient (7.6%) had undergone prior radiotherapy treatment in the injury group, while the neoadjuvant chemotherapy drug was used in 8 cases in the injury group (61.5%) and 11 in the control group (42.3%).

Five (38.0%) versus 13 (50.0%) cases were in the I-II postoperative staging, while the 8 remaining cases (61.5%) versus 13 cases (50.0%) were in the Ep III-IV.

Based on Table 1, we can observe that only the variable 'presence of axillary metastasis adhered to axillary vessels' (Meta ava) showed a 1% difference of significance (or 99% of confidence) regarding the answer variable "injury". In other words, patients with presence of axillary metastasis adhered to axillary vessels showed a higher rate of injuries, while patients without such characteristic had a smaller volume.

After using the logistic regression technique, we found that only the variable "axillary incision separated from the breast incision" (InA-InM) is not significant at a 5% level and, therefore, is removed from the mathematical model. The other variables were significant and remained (p-value was smaller than 0.0001 in all of them). Being significant in a regression model reports that the variable is associated with the answer variable, i.e. explains a percentage of the answer variable. Figure 1 presents the model equation.

Based on it, the most important variable that best explains the answer variable is the "presence of axillary metastasis in the perioperative period" (Meta trans-op), followed by "postoperative staging" (Est_Pos-IIIB), according to Figure 2.

This model presented positive and validation rates of 96.26 and 97.00% respectively, as verified in Figure 1. Its predictive value was 96.26%, which is an excellent result on practice. Positive and negative predictive results were also great. The sensitivity and specificity measures presented high values; therefore, the logistic regression model is classifying subjects regarding the presence or not of the answer variable "injury" as correctly.

Table 1. Results of chi-square tests with each variable associated with injury to the axillary vein during lymphadenectomy.

Variables	Chi-square	p-value	Result	Conclusion
Meta pre-op	0.3312	0.5650	It accepts H_0	No significant difference
BLS pre-EA	0.2216	0.6378	It accepts H_0	No significant difference
Meta trans-op	2.2029	0.1378	It accepts H_0	No significant difference
Meta ava	6.8954	0.0086	It rejects H_0	Significant difference
TM (cm)	0.1088	0.7415	It accepts H_0	No significant difference
IMP	1.9152	0.1664	It accepts H_0	No significant difference
RMPM	0.0659	0.7974	It accepts H_0	No significant difference
InA-InM	0.0132	0.9084	It accepts H_0	No significant difference
RXT pre	2.2503	0.1336	It accepts H_0	No significant difference
QT neo	0.0530	0.8179	It accepts H_0	No significant difference
Est pos-op	0.4643	0.4956	It accepts H_0	No significant difference

Meta pre-op: presence of palpable axillary metastasis at preoperative examination; BLS pre-EA: research of sentinel lymph node before axillary lymphadenectomy; Meta trans-op: presence of axillary metastasis identified at perioperative period; Meta ava: axillary metastasis adhered to the axillary vessels; TM (cm): size of the axillary metastasis in the perioperative period in centimeters; IMP: presence of axillary metastases invading the pectoralis major muscle; RMPM: resection of the pectoralis minor muscle during axillary lymphadenectomy; InA-InM: axillary incision separated from the breast incision; RXT pre: radiotherapy prior to surgery; QT neo: neoadjuvant chemotherapy; Est pos-op: postoperative staging.

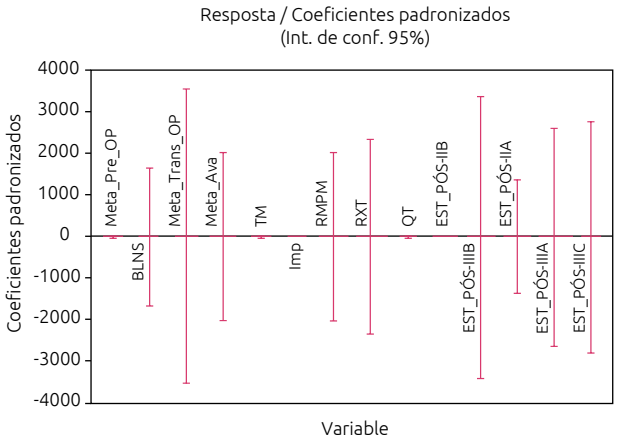

Figure 2. Explanation of each variable.

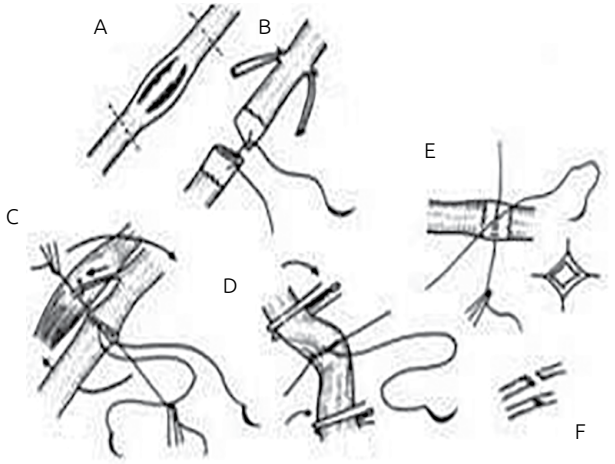

Figure 3. Vascular sutures.

DISCUSSION

Every axilla with palpable lymph nodes should be emptied[16]. The only situation where axillary lymphadenectomy is not currently indicated is the presence of breast ductal carcinoma in situ, although it has a risk of axillary metastases from 0.9 to 3.8%, according to several authors[17,18]. Another subgroup with low potential of axillary metastases is microinvasive carcinoma. Most of the papers[19,20] show a 5% incidence of axillary metastases, even though Schuh et al.[21] and Kinne et al.[22] found axillary damage rates between 20 and 10%, respectively. The different definitions of what a microinvasive or invasive tumor is would result in this frequency variation of the axillary metastasis process.

The incidence of axillary damage is closely associated with the size of the primary tumor, which is 68% in patients measuring between 1 and 2 cm of diameter, with presence of lymphatic or vascular invasion[23].

Local control of breast cancer also results in increase of survival and incapacity of "cleaning" the axilla may result in difficulties to manage the disease, with distant metastases, as observed in the NSABP B-04[24] study. The incorporation of the sentinel lymph node investigation in the breast neoplasm treatment has provided many benefits to women at early stage of the disease, limited to the breast, thus avoiding axillary lymph node dissection. This treatment substantially reduced the risk of functional sequelae in the arm, which is the result of surgical manipulation, and morbidities, which cause high social, psychological, and financial costs[25].

Surgical aggressive behavior is a risk factor for the development of significant morbidity, which also explains higher

incidence of lymphedema in the postoperative period of mastectomy than in the conservative surgery (24 to 49% after mastectomy, and 4 to 28% after tumorectomy with axillary dissection)[26]. An explanation would be that patients who undergo mastectomy, in general, present an advanced disease with the need of larger surgical removal of axillary lymph nodes, which are more compromised by the tumor. After surgery, weight gain may also be a risk factor[27].

The dissection of axillary lymph nodes and the amount of resected and damaged lymph nodes are well known risk factors for the development of lymphedema and, at a rare scenario, injury or thrombosis of axillary vein[28-30].

Vascular injuries are very important complications due to the potential risk of thrombosis, arteriovenous fistula (AV), pseudoaneurysm, functional loss of extremities, amputation, infections, and bleeding[31,32].

In the beginning of the 20th century, vessel ligation was the only kind of performed intervention, whose purposes were hemostasis or treatment of AV fistulae or aneurysms[33].

Consequently, the development of anesthetic techniques, the anticoagulant possibility, blood transfusions enabling its replacement in large-sized vascular surgeries, the discovery of antibiotics suppressing a great part of the failures caused by infection and the improvement of industrial prosthetics provided a golden phase of development to the vascular surgery[34].

Vessel dissection is done with common instruments to any dissection until arrival of the vessel, such as: scalpel, Metzenbaum scissors of variable size and blunt tip, rat-tooth forceps, vascular dissection clamps, and Mixter clamps with tips whose thicknesses should vary according to the kind and caliper of the dissected vessel. Anatomic knowledge of the operated area is mandatory, because orientation, in the event of an obstruction with absence of heart rate, should be given by neighboring elements[35].

The incision of access is longitudinally to the vessel path. After skin, subcutaneous, fascia and separation of the muscles, we arrive at the vessel, which is always involved by a fiber adipose sheath. We may open this sheath with the help of a vascular dissection clamp and Metzenbaum scissors until reaching the vessel adventitious plane, which is followed proximal and distally up to the desired length of dissection[36].

Vascular ligations are performed for simple hemostasis in cases of trauma, amputations, venous resections, and AV fistulae ligation. In the event of small vessels, a simple ligation is enough; if the vessel is larger, a transfixing suture may be performed. If the vessel must be sectioned, do it between ligations through transfixation. In cases of larger vessels (above 5 mm), perform a running suture. This suture may eventually be protected by a ligation[35].

We do not need anticoagulation when an artery is ligated definitely; the formation of a thrombus is foreseen that will extend until the first important proximal branch. However, when the interruption of the artery or vein is temporary, one may anticoagulant the patient with intravenous heparin in the dose of 1.5 mg or 150 units/kg of weight to promote surgical approaches on them. Half of this dose may be repeated after about two hours if the surgeon notices the formation of clots on the field. After the procedure ends, we reverse the heparin effect with protamine sulfate in the proportion of 1:1 mg in relation to the heparin dose[37].

Vascular sutures should include all wall layers, and they can be done with running structure or separated sutures. The distance between the points should be 1 mm, with a 1 mm depth. In general, we use 3-0 to 6-0 surgical sutures. Running suture should be made with two surgical sutures that begin in each junction and direct to the middle of the incision (Figure 3). The separated point suture, otherwise, should be used with small caliper vessels. The path must be large enough to avoid stenosis, but not so large to cause vessel enlargement, which could result in undesirable hemodynamic alterations[35].

Among the 13 mentioned cases, we observed the importance of staging in the incidence of axillary metastases: 30.7% of axillary damage in stage IIIC; 23% in stage IIIB; 7.6% in stage IIIA; and 15.3% in stage IIB. We found that axillary damage is closely associated with the primary tumor size, and it is a common event (a third of cases) as well as the most important prognosis factor. Other predictive variables of axillary metastasis, besides the tumor size, include: age, lymphatic vascular invasion, histological type, nucleal degree, histological degree, tumor grade, and location.

CONCLUSION

There are currently few studies in literature on the theme, even though much is discussed about the lymphedema, the main postoperative complication in breast surgery. Many factors have been discussed, but studies clarifying the influence of each one in the formation of lymph-lymphatic anastomosis, in compensations of the lymphatic system and in consequent repercussions on the incidence of the lymphedema still lack.

This study showed that the presence of axillary metastases in the perioperative evaluation, as well as adhered to axillary vessels, is associated with an increased risk of axillary vein injury during the axillary lymphadenectomy.

Injury or axillary vein thrombosis and injury to the axilla motor nerves are extremely rare complications. A careful surgical technique and accurate selection of patients for postoperative radiotherapy are mandatory to prevent significant morbidity after axillary lymphadenectomy. The introduction of the sentinel lymph node biopsy technique in clinical practice resulted in a significant decrease of the incidence of post-axillary lymph node dissection complications.

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Appendix 1. Data collection form

AXILLARY VEIN INJURY DURING LYMPHADENECTOMY– ASSOCIATED FACTORS

01. Patient's identification:

Registration:[_____] Age:[____] years old (in the date of diagnosis)
Date of the new case:___/___/___ BMI:_____

02. Presence of palpable axillary metastasis at preoperative examination

03. Preoperative staging

04. Treatment

04.1 Surgery

(1) Biopsy of the sentinel lymph node before lymphadenectomy
(2) Presence of axillary metastasis in the perioperative period
(3) Presence of axillary metastasis adhered to axillary vessels
(4) Size of axillary metastasis in the perioperative period
(5) Presence of pectoralis muscle invasion
(6) Preservation or section of the pectoralis major muscle
(7) Axillary incision separated from the breast incision

04.2 Radiotherapy prior to surgery

04.3 Neoadjuvant chemotherapy

05. Postoperative staging

Notes:_____

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ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND BREAST CANCER DEVELOPMENT: A CASE-CONTROL STUDY

Associação entre ingesta alcoólica e desenvolvimento de câncer de mama: um estudo de caso-controle

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ABSTRACT

Objectives: To identify the association of alcohol consumption with the development of breast cancer in a patient population of Salvador, Bahia. **Methods**: Case-control study, conducted between December 2013 and May 2015, with 69 patients with breast ductal carcinoma and 71 controls. Sample calculation was made with 140 patients, with 5% presumed difference between groups and 10% acceptable difference. The x^2 test was used to evaluate the correlation between categorical variables, and Student's *t*-test was applied to compare continuous variables. **Results**: From all cases, medium alcohol intake was 3.66±8.60 g/day; among controls, the average was 3.71±7.40 g/day (p=0.890). When analyzing the association between alcohol intake and breast cancer, odds ratio was 0.99 (95% confidence interval 0.524–1.890), p=0.988. For alcohol consumption greater than 10 g/day and breast cancer, odds ratio was 1.579 (95%CI 0.624–3.995), p=0.332. **Conclusions**: Although published data suggest an association between alcohol consumption and breast cancer, in this study there was no statistical significance between the variables assessed and the onset of this pathology.

KEYWORDS: Breast neoplasms; risk factor; primary prevention; risk groups.

RESUMO

Objetivo: Identificar a associação do consumo alcoólico com o desenvolvimento de câncer de mama em uma população de pacientes de Salvador, Bahia. **Métodos**: Estudo de caso-controle realizado entre dezembro de 2013 e maio de 2015 com 69 pacientes com diagnóstico de carcinoma ductal da mama e 71 controles. Foi realizado cálculo amostral com 140 pacientes, esperando-se uma diferença presumida de 5% entre os grupos e com diferença aceitável de 10%. Realizou-se teste do x^2 para avaliação de correlação entre as variáveis categóricas e teste *t* de Student entre as variáveis contínuas. **Resultados**: Entre os casos, a ingesta alcoólica média foi de 3,66±8,60 g/dia; já entre os controles a média foi de 3,71±7,40 g/dia (p=0,890). Ao analisar-se a associação entre ingesta alcoólica e câncer de mama, obtivemos *odds ratio* de 0,99 (intervalo de confiança de 95% – IC95% 0,524–1,890), p=0,988. Em relação ao consumo de álcool maior do que 10 g/dia e câncer de mama, a *odds ratio* foi de 1,579 (IC95% 0,624–3,995), p=0,332. **Conclusão**: Apesar de dados publicados e hipóteses sugerirem associação entre ingesta alcoólica e câncer de mama, neste estudo não houve significância estatística entre as variáveis analisadas e a presença da patologia.

PALAVRAS-CHAVE: Neoplasias da mama; fator de risco; prevenção primária; grupos de risco.

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INTRODUCTION

Breast cancer is the most common malignancy among women worldwide, with about 1 million new cases each year[1,2]. Its incidence has increased over time in association with industrialization and urbanization[3]. Although breast cancer is considered a carcinoma with relatively good prognosis if diagnosed and treated early, mortality rates remain high in Brazil, possibly because in some cases diagnosis is only made in advanced stages. Its etiology is not yet fully understood; however, some features have been proven to be related to its onset, including genetic, environmental, hormonal, and biopsychosocial factors[1,2,4].

Some studies suggest a mild association and dose/response relationship between alcoholic intake and breast cancer, pointing out the consumption of 10 g/day as a factor predisposing to its development[5,6]. These papers show that there is not a single mechanism that explains such association.

The evidence points that alcohol increases estrogen levels, a well-known risk factor for breast cancer. This hypothesis is supported by data showing the association between alcohol and breast cancer limited to women whose tumors present positive estrogen receptor (ER +)[7].

Other studies indicate that alcohol can increase the risk of breast cancer by other means, depending or not on hormones, such as the cocarcinogenic action resulting from the increased capillary permeability in cell membrane to carcinogens, inhibiting detoxification by the liver, impairing nutrient metabolism, and inducing oxidative stress[1,8].

Derivatives of alcohol metabolism such as acetaldehyde are responsible for changes in DNA that are also related to the disease development[9].

As alcohol consumption increases worldwide[5], especially in regions where female emancipation has been noticeably occurring, a better understanding of mechanisms linking this behavior to breast cancer is desirable. The present study aimed to assess alcohol consumption as a risk factor for the onset of breast cancer in patients from a mastology and an oncology clinics in Salvador, Bahia.

METHODS

Case-control study conducted from December 2013 through May 2015. Data were collected from medical records, complementary interviews, and questionnaire application at two clinics in Salvador, Bahia, which assist patients enrolled in private health insurance plans: Oncology Center of Bahia (*Núcleo de Oncologia da Bahia*), an oncology clinics, and Breast Center (*Núcleo da Mama*), a mastology clinics.

Adult women with histopathological diagnosis of breast cancer in its main variant, invasive ductal carcinoma, either by core biopsy or surgical specimen, were included in case group as systemic treatment "debuts". The control group allocated women without breast cancer in follow-up at the mastology clinics after the disease was ruled out by mammography and/or ultrasonography. Patients from both groups were paired by age, with difference of no more than five years.

Patients who had been through any oncological treatment before or started a treatment at some point before data collection were excluded from the case group. In control group, patients with BIRADS category scale 3, 4 and 5 who needed a biopsy resulting in any type of change that could increase breast cancer risk were excluded: moderate or florid ductal hyperplasia, intraductal papilloma, sclerosing adenosis, complex fibroadenoma radicular scar, complex sclerosing lesion, lobular neoplasia/atypical lobular hyperplasia, atypical columnar cell changes, atypical ductal hyperplasia, flat epithelial atypia, cystic lobular hyperplasia, clinging carcinoma, blind ductal adenosis, microcystic adenosis, and microglandular adenosis. Patients who refused to sign the Informed Consent Form were also excluded from the study.

For this study, beer was considered to have 5% alcohol in its composition; vodka, 40%; wine, 12%; and whiskey, 40%[10]. The calculation used for the amount of alcohol ingested by patients was the volume ingested multiplied by alcohol concentration in each beverage: for example, 350 mL of beer × 5% alcohol = 17.5 g of alcohol ingested.

Statistical analysis was made in the program Statistical Package for the Social Sciences (SPSS) v. 20.0. Numerical variables were expressed as mean and standard deviation. Percentage was calculated for descriptive variables. Continuous variables were compared by Student's t-test. The χ^2 test was used to assess correlation between categorical variables, including the relationship between alcohol intake and breast cancer development, and between 10 g/day alcohol consumption and breast cancer development. In order for results to be considered statistically significant, two-tailed values should have $p<0.05$.

The study was approved by the Research Ethics Committee (CEP) of Bahia Foundation for the Development of Sciences, opinion 140,996 and report in October 31, 2012.

RESULTS

A total of 140 patients were recruited, 69 having a proven diagnosis of ductal breast carcinoma and 71 being controls.

Overall characteristics of cases and controls did not show statistically significant differences (Table 1). Mean age of cases was 56.67±12.91 compared to 53.41±10.30 of controls. Regarding ethnicity, almost half of patients with breast cancer declared themselves as brown-skinned (47.8%), while 11.6% as black-skinned, and 40.6% as white-skinned. Among patients in control group, 46.5% declared themselves as brown-skinned;

18.3%, black-skinned; and 25.0% white-skinned. The mean age at menarche was 12.79±1.93 in case group and 13.07±1.78 in control group.

As to family history, 11.6% of patients in case group reported a first-degree relative (mother, sister or daughter) with breast cancer, compared to 16.9% in control group.

After subanalysis, only 29.0% of patients in case group were found to consume alcoholic beverages, while alcohol intake was positive in only 33.8% of patients in control group. Regarding type of alcoholic beverage ingested, case group had the following values: 65% beer; 20% wine; 10% whiskey; and 5% vodka. For control group, we had: 87.5% beer; 8.3% wine; and only 4.2% vodka.

When frequency of alcohol consumption was assessed, the case group had 35% of patients reporting drinking only once a week; 60% twice a week; and 5% three times or more per week. In control group, 50% reported drinking once a week and 50%, twice a week. In this group, no reference to alcohol consumption three times or more per week was made. The patterns of alcohol consumption of the sample are shown in Table 2.

Mean alcohol consumption, object of this study, was 3.66±8.60 g/day in the case group and 3.71±7.40 g/day in the control group, which configures a non-statistically significant difference (Table 3).

Table 4 shows the estimated risk of breast cancer when alcohol intake is the exposure variable. When analyzing, therefore, the association between alcohol consumption and breast cancer, odds ratio (OR) was 0.995 (95% confidence interval 0.524-1.890), p=0.988. Also, no statistical significance.

As some studies suggest a mild association between alcohol consumption greater than 10 g/day and breast cancer onset[5,6], the estimated risk for this neoplasia with 10 g/day of alcohol intake as exposure variable was calculated. OR was 1,579 (95%CI 0.624-3.995) and p=0.332, as shown in Table 5.

Table 1. Clinical profile of patients.

	Patients with breast cancer (n=69)	Controls (n=71)	P value
Age (year), mean ± standard deviation	56.67±12.91	53.41±10.30	0.101
Self-reported skin color			
White, n (%)	28 (40.6)	25 (35.2)	0.510
Brown, n (%)	33 (47.8)	33 (46.5)	
Black, n(%)	8 (11.6)	13 (18.3)	
Age at menarche (year)	12.80	13.07	0.386
Breast cancer family history			
Yes	8 (11.6)	12 (16.9)	0.365
No	61 (88.4)	59 (83.1)	

DISCUSSION

According to the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR)[1], alcoholic beverages intake is a risk factor for the development of breast cancer in both premenopausal and postmenopausal periods.

This study did not find association between alcohol consumption and breast cancer. Our findings are believed to be the consequence of several limiting factors such as: memory bias, since patients tend to remember the most recent intake; small number of cases and controls reporting intake greater than 10 g/day; and patients mentioning champagne, prosecco and other types of alcoholic beverages.

Table 2. Patterns of alcohol consumption in the sample.

Characteristics (variables)	Cases n (%)	Controls n (%)
Alcohol intake		
Yes	20 (29)	24 (33.8)
No	49 (71)	47 (66.2)
Frequency of alcohol intake		
Once a week	7 (35)	12 (50)
Twice a week	12 (60)	12 (50)
Three times or more per week	1 (5)	0
Type of beverage		
Beer	13 (65)	21 (87.5)
Wine	4 (20)	2 (8.3)
Whiskey	2 (10)	0
Vodka	1 (5)	1 (4.2)

Table 3. Alcohol intake (in grams) per day.

Cases mean ± standard deviation g/day	Controls mean ± standard deviation g/day	P value
3.66±8.60	3.71±7.40	0.890

Table 4. *Odds ratio* for breast cancer with alcohol intake as exposure variable.

Variable	*Odds ratio*	95CI%	P Value
Alcohol intake	0.995	0.524–1.890	0.988

95%CI: 95% confidence interval.

Table 5. *Odds ratio* for breast cancer with alcohol intake >10 g/day as exposure variable.

Variable	*Odds ratio*	95CI%	P Value
Alcohol intake >10 g/day	1.579	0.624–3.995	0.332

95%CI: 95% confidence interval.

Although the present study did not show statistical significance, some studies[8,9,11-13] confirm the risk effect represented by alcoholic beverages. Setiawan et al.[11], in a cohort study involving 84,427 women, evaluated the association between alcohol consumption and breast cancer according to their hormonal receptors' status. Relative risk (RR) of 1.71 (95%CI 1.19-2.46) was found comparing alcohol intake (equal to or greater than two doses/day) and no intake of alcohol among patients with ER/PR (estrogen receptor/progesterone receptor) breast cancer. For ER/PR + type of cancer, RR was 1.40 (95%CI 1.14-1.72). These RR values were not statistically different (p=0.07), indicating that positive or negative hormone receptors did not pose change to the risk.

In a case-control study conducted in Italy, Deandrea et al.[8] stated that alcohol consumption greater than 13.8 g/day increased the risk of breast cancer compared to women who never drank alcohol, with OR 1.96 and 95%CI 1.57-2.47. However, when the analysis was performed according to the hormone receptors' status, risk effect was only found for breast tumors with positive estrogen receptors. According to these authors, the risk of breast cancer onset in the presence of alcohol consumption is more related to positive estrogen receptors. In-vitro studies have identified ethanol activity in human breast cells with positive but not negative estrogen receptors[8,12].

In a cohort conducted with 38,454 women in the United States, Zhang et al.[12] assessed the risk effect of alcohol consumption in in-situ and invasive breast cancers. When analyzing according to hormonal receptors' status and considering 10g/day alcohol intake, an increased risk for breast cancer was pointed only for ER/PR+ tumors. In addition, the consumption of 10 g/day caused a 7% increase in the risk of in-situ breast cancer (RR=1.07; 95%CI 1.01-1.14) and 9% of invasive breast cancer (RR=1.09, 95%CI 1.02-1.16). Important to point out that the increased risk was analyzed for beer, since this was the type of alcoholic beverage consumed in the sample in question.

In a cohort study with 88,530 postmenopausal women in the United States, Duffy et al.[9] identified that even low alcohol intake (5.6 g/day) may be considered a risk factor for breast cancer, with RR=1.05; 95%CI 1.01-1.09.

Berstad et al.[13] conducted a case-control study in the United States to analyze alcohol consumption according to type of beverage and time of ingestion. Significant association was found only for intake greater than or equal to two doses/day in the previous five years (OR=1.82, 95%CI 1.01-3.28). This study found no relation to consumption in other periods of life: adulthood or youth. As to the outcome of this case-control, we can consider the memory bias, since people tend to remember recent events of alcohol intake; or that the effect of alcohol on the risk for breast cancer is not accumulative over time. No significant differences were found between as to different types of beverages mentioned by women, thus indicating that ethanol relates to increased risk for such neoplasia regardless of different types ingested[12,13].

Differently from the results presented, a case-control study conducted in France by Bessaoud et al.[14] identified daily alcohol consumption of 10-15 g/day as a protection factor against breast cancer, compared to women who do not use alcohol (OR=0.21, 95%CI 0.10-0.91). The protective effect was identified for both moderate wine intake (<1 dose /day) (OR = 0.51, 95%CI 0.30-0.94) and other beverages (OR=0.63, 95%CI, 0.42-0.94). Especially relating to the protective effect of wine, the harmful effect of alcohol is suggested to be partly diminished because of antioxidant agents from the grape present in the beverage, considering moderate consumption[14].

However, although some studies suggest that alcohol acts as a risk factor and one suggests it is a protective factor, Terry et al.[15] and Brown et al.[16], after conducting case-control studies, did not identify significant associations between this variable and breast cancer onset, similarly to the results of our study.

The lack of association was partially explained by the homogeneous pattern of consumption as to type of beverage and the low alcohol intake among women in the sample. In addition to contradictory findings when studies are compared, data are not consistent with regard to the association between this neoplasm and alcohol consumption according to hormonal receptors' status, type of cancer, amount of alcohol ingested, and the period of exposure to alcohol[12,14].

Some studies have also identified the influence of skin color on breast cancer onset[17,18]. The incidence may be higher among Caucasians and African Americans, intermediate among Hispanics and Amerindians, and low among Asians[17,19]. The miscegenation in Brazil, especially in Bahia, is highly likely to influence the development of breast cancer, which justifies the need for further specific studies on this population[17,20]. Studies assessing variables and risk factors for this heterogeneous population have not yet been published, neither are there models — like Gail's[21] — that calculate the risk of breast cancer among Brazilian women.

Among the limitations of this study, its case-control design may be mentioned, as it is not ideal, although it has been adopted in view of its feasibility; the low number of patients who consumed alcohol three times or more per week (only one in case group and none in control group). Despite all that, when analyzing women who would consume alcohol above the mark of 10 g/day, the percentages in case and control groups were 18.3% and 9.8%, respectively. Would these values be statistically significant had the number of participants been larger? This and other questions posed by the present study require a response for more accurate information and orientation about breast cancer prevention for Brazilian women.

CONCLUSION

Although there is scientific evidence to prove the association between alcohol consumption and breast cancer, the present study did not found this relationship.

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CORRELATION BETWEEN ULTRASONOGRAPHIC FEATURES AND HISTOPATHOLOGICAL FINDINGS OF BREAST LESIONS IN BIOPSIES

Correlação entre características ultrassonográficas e achados histopatológicos de lesões mamárias em biópsias

Laila Carolline Freitas e Silva[1]*, Josmara Ximenes Andrade Furtado[2]

ABSTRACT

Imaging exams are fundamental tools to characterize palpable lesions and to early detect those not identified on the physical examination. However, the correct interpretation of these findings should be done by correlating them with the probable histological diagnosis of the lesion, and performing the appropriate treatment in a timely manner. The Breast Imaging-Reporting and Data System (BIRADS®) is the system used for this association, which characterizes the findings in mammography, ultrasonography and mammary magnetic resonance images, classifying them according to the probability of malignancy. **Objective:** To correlate imaging features of breast nodules, evidenced by ultrasonography and classified according to BIRADS®, with the histopathological examination results of material obtained through thick needle biopsy of patients from the mastology ambulatory of the Maternity School Assis Chateaubriand that confirm this predictive value of the imaging examination and the impact on surgical indications. **Results:** We analyzed 110 patient's medical records that fit the inclusion criteria and found that more than 97% of lesions with low suspicion of malignancy, BIRADS® 4A, presented a benign histopathological result. However, all patients with images of nodules with high suspicion of malignancy had histopathological diagnosis of invasive carcinoma. In conclusion, the ultrasonographic features of breast lesions have high predictive value in the final diagnosis of the lesion, supporting the decision of conduct in adequate time in each situation.

KEYWORDS: Ultrasonography, mammary; breast; biopsy, needle.

RESUMO

Os exames de imagem são ferramentas fundamentais na caracterização de lesões palpáveis e na detecção precoce daquelas não identificadas ao exame físico. Porém, é necessária a interpretação correta desses achados, correlacionando com o provável diagnóstico histológico da lesão, realizando tratamento adequado e em tempo certo. O *Breast Imaging-Reporting and Data System* (BIRADS®) é o sistema utilizado para essa relação, caracterizando os achados em imagens de mamografia, ultrassonografia e ressonância magnética mamária e classificando-os de acordo com a probabilidade de malignidade. **Objetivo:** Correlacionar características imagenológicas de nodulações mamárias, evidenciadas por ultrassonografia e classificadas de acordo com o BIRADS®, com os resultados dos exames histopatológicos de material obtido através de biópsia de agulha grossa de pacientes do ambulatório de mastologia da Maternidade Escola Assis Chateaubriand, confirmando esse valor preditivo do exame de imagem e o impacto nas indicações cirúrgicas. **Resultados:** Foram analisados 110 prontuários de pacientes que se encaixavam nos critérios de inclusão e constatou-se que mais de 97% das lesões com baixa suspeição de malignidade, BIRADS® 4A, apresentaram resultado benigno no exame histopatológico. Entretanto, todas as pacientes com imagens de nódulos com alta suspeição de malignidade tiveram diagnóstico histopatológico de carcinoma invasor. Pode-se concluir que as características ultrassonográficas das lesões mamárias têm alto valor preditivo no diagnóstico final da lesão, fundamentando a decisão de conduta em tempo adequado em cada situação.

PALAVRAS-CHAVE: Ultrassonografia mamária; mama; biópsia por agulha.

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INTRODUCTION

The detection of breast nodules for diagnosing cancer precursor lesions before clinical manifestations is essential, considering its early discovery allows a less aggressive treatment and yet more effective for these diseases.

In recent years, imaging studies have greatly aided in the screening of non-palpable breast lesions, with emphasis on mammography, which identifies micro-calcifications, asymmetries and nodules, and on mammary ultrasonography, which is the most commonly used complementary method to characterize mammographic findings or to assist in the investigation of dense breasts.

These findings must be standardized regarding the conduct, mainly based on the morphological characteristics of the lesions found in the imaging tests. To this end, the American College of Radiology, the National Cancer Institute (NCI), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the American College of Surgeons and the American College of Pathologists have created a system to standardize radiology reports when analyzing breast imaging, the Breast Imaging-Reporting and Data System (BIRADS®).

The importance of this classification is mainly due to the easy way of separating benign lesions from potentially malignant lesions (according to their mammographic, ultrasonographic or magnetic resonance features) and their acceptable correlation with the histopathological findings.

The identification of lesions suspected of malignancy determines the need of cytological or histopathological evaluation through a minimally invasive procedure, whose arsenal consists basically of fine-needle aspiration (FNAB) or core-biopsy; in discordant cases, the open biopsy is used to determine the definitive diagnosis of the lesion[1-3].

Current data point to reliability of the BIRADS® classification for the professional in making decisions regarding the conduct of breast lesions, based on the possibility of a particular lesion being benign or malignant, and in analyzing its imaging features in order to treat each patient properly and in time.

The purpose of this study is to correlate the imaging findings of breast lesions with a definitive diagnosis confirmed by a histopathological study, demonstrating the high predictive value of the BIRADS® classification and evaluating the impact of these findings on surgical intervention. Moreover, this correlation between the two exams may avoid unnecessary procedures, as to typically benign lesions, or may alert to the urgency of treatment in those with higher chances of malignancy, according to the imaging characteristics.

The aim of this study was to correlate imaging features of breast nodules, evidenced by ultrasonography and classified according to BIRADS®, with the results of histopathological examination of materials obtained through thick-needle biopsy and incisional biopsy, when performed, of patients from the outpatient clinic of mastology at the Maternity School Assis Chateaubriand.

METHODS

Type of study and sample

This is a retrospective, quantitative and descriptive study carried out through the record evaluation from patients attended at the Outpatient Clinic of the Maternity School Assis Chateaubriand who underwent breast biopsy using a thick needle between January 2015 and January of 2016. We searched the medical records from 136 patients seen at the Benign Pathology Clinic of the institution.

Data collection and analysis

The procedures recorded in the Ultrasonography Service were cataloged according to the performance of ultrasound guided biopsy, excluding FNAB and pre-surgical marking of the impalpable lesion, obtaining a list of medical records that would be analyzed.

A specific form was applied with clinical-epidemiological questions of the patients and evaluation of the imaging characteristics of the breast nodules seen in the ultrasonography, as well as the result of the histopathological examination.

The collected data were stored in tables in the Microsoft Excel program for correlation of the values, which were later statistically analyzed. The graphs and tables of the present study were also generated in the same program.

Inclusion criteria

Patients who underwent thick needle biopsy in the Ultrasonography Service of the Maternity School Assis Chateubriand were evaluated at a subsequent medical visit for the results of the anatomopathological report and pertinent conduct guidance.

Exclusion Criteria

Patients with incomplete data on the patient's medical record were excluded from the study, such as absence of a pathological examination result and non-BIRADS® ultrasonographic classification in the exam that generated the biopsy request, or patients who abandoned treatment/follow-up at the institution, as well as patients who underwent FNAB. In total, 26 patients were excluded.

Ethical aspects

The Maternity School Assis Chateaubriand Research Ethics Committee approved the project, with approval number 1.869.537.

RESULTS

Patient population

We analyzed 110 medical records that fit the inclusion criteria. According to the ultrasonographic features of breast lesions, only one case was classified as BIRADS® 2 (biopsy due to the patient's personal history), corresponding to 0.9% of the total; 46 cases (41.8%) were classified as BIRADS® 3; 55 (50%) as BIRADS® 4, thus

distributed into: 4A in 32.7%; 4B in 9.1%; 4C in 2.7%; and 5.4% without described subdivision (Figure 1). Furthermore, eight cases (7.7%) were classified as BIRADS® 5. Among the patients with BIRADS® 3, all the histopathological results were from benign breast lesions.

After evaluating the medical records, we observed that the mean age of the patients who entered the inclusion criteria for the study was 46.09 years.

Only 11% of the patients had a family history of breast cancer and 3.6% had a personal history of the disease. Patients who underwent mammography presented BIRADS® 0 classification in 42.7% of the cases, suggesting diagnostic complementation for having presented lesion to this method. Most of the biopsied lesions were impalpable (59.1%) and about 42.7% underwent surgery to remove the nodule.

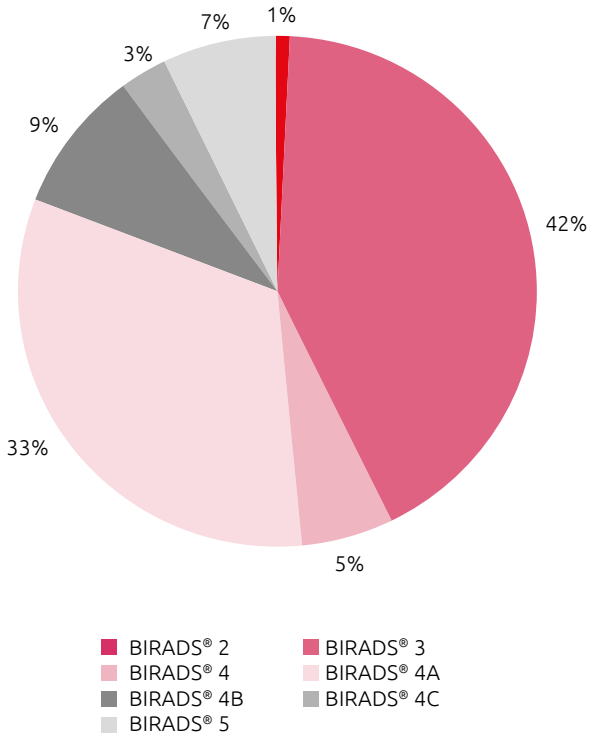

Figure 1. BIRADS® ultrasonographic classification of the study patients.

BIRADS® 3 Group

Patients with solid breast lesions with regular, circumscribed margins, precise limits and no posterior acoustic shade were classified as BIRADS® 3. The mean age of these patients was 44.06 years. All the lesions presented benign features in the biopsy result, as well as in the product of the surgical specimen of the lesions (Figure 2).

Approximately 21.7% of the patients underwent surgical excision of the lesion, and benign lesions were found in all cases (seven fibroadenomas, one adenosis, one benign phylloid tumor and one fibrosis).

Most of the lesions were impalpable; that is, they were detected only in imaging tests (69.6%). Approximately 47.8% of the patients who underwent mammography were classified as BIRADS® 0, suggesting the conduction of ultrasonography.

IRADS® 4 Group

Breast nodules presenting lobular or irregular margins, poorly defined limits, presence of posterior or lateral acoustic shadow and cystic areas were classified as BIRADS® 4, which were subdivided into A, B or C, depending on the degree of these features.

In some records, this sub-classification was omitted by the examiner or radiologist who made the examination report; these patients accounted for 5.4% of the sample. In half of the cases, the histopathological result of the biopsy and surgical specimen was invasive breast carcinoma; the other half resulted in benign lesions.

The lesions subclassified as BIRADS® 4A also presented benign lesions in the histopathological analysis, with a total of 97.3% of

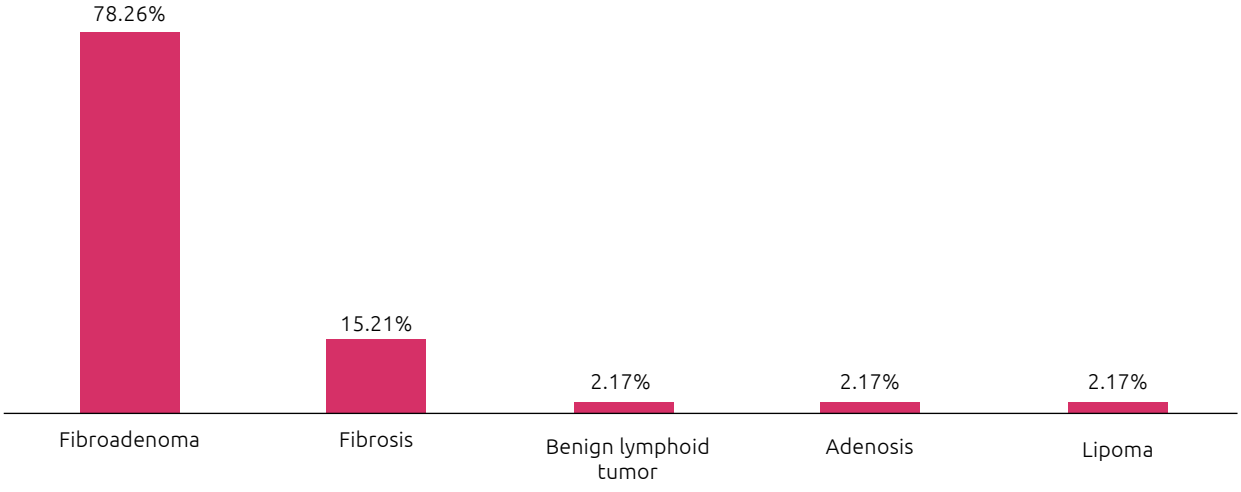

Figure 2. Histopathological results of lesions classified as BIRADS® 3.

the findings (Figure 3). Only one patient presented a complex sclerosing proliferative lesion in the thick needle biopsy, which later confirmed carcinoma in situ in the surgical specimen. In approximately 75% of the patients, the lesion was impalpable.

Nodules with characteristics of moderate suspicion, classified as BIRADS® 4B, represented 9.1% of the sample. Of the thick needle biopsies, 50% resulted in invasive carcinoma after histopathological analysis, 10% of lesions were at risk and 40% of benign lesions. After surgical removal of the lesions, a case of flat epithelial atypia, diagnosed in fragment biopsy, presented areas of invasive carcinoma in the surgical specimen (Figure 4). The majority of cases (60%) were of impalpable lesions and 30% were also classified as BIRADS® 4 on mammography.

Only 2.7% of the patients had a breast lesion classified as high suspicion of malignancy (BIRADS® 4C). In all cases, invasive carcinoma was diagnosed in the thick needle biopsy and in the surgical specimen. The lesions were all palpable, although only one-third were larger than 2 cm in size at ultrasonography.

BIRADS® 5 Group

A little more than 7% of the patients presented lesions with ultrasound characteristics highly suggestive of breast neoplasm, classified as BIRADS® 5. Only one case did not confirm invasive carcinoma, resulting in fibrosis (Figure 5). All lesions were palpable, although 87% measured between 1 and 2 cm by imaging examination. About 37.5% of the mammograms also presented a highly suspected lesion.

DISCUSSION

According to the sixth edition of the BIRADS® system, the lesion categories are divided as follows:

- Category 0: needs additional imaging or previous exams for comparison;
- Category 1: negative;
- Category 2: benign findings;
- Category 3: probably benign;

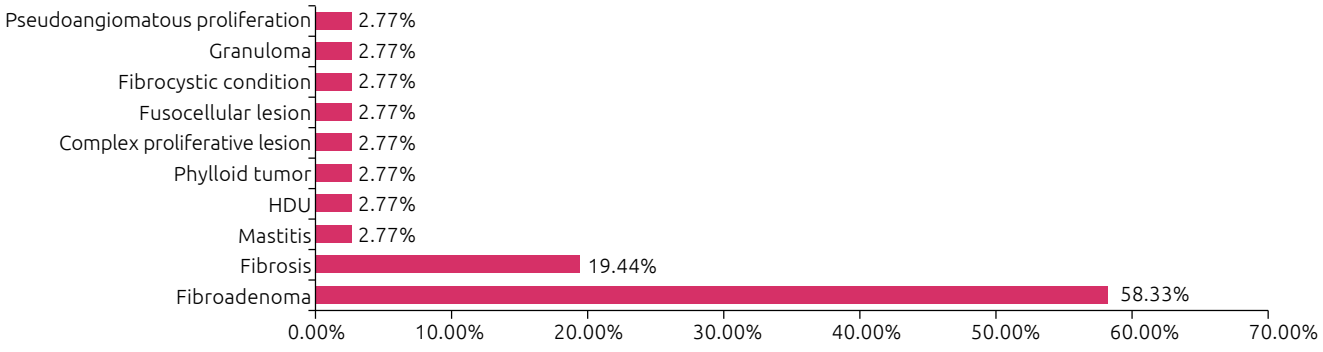

Figure 3. Histopathology of lesions classified as BIRADS® 4A.

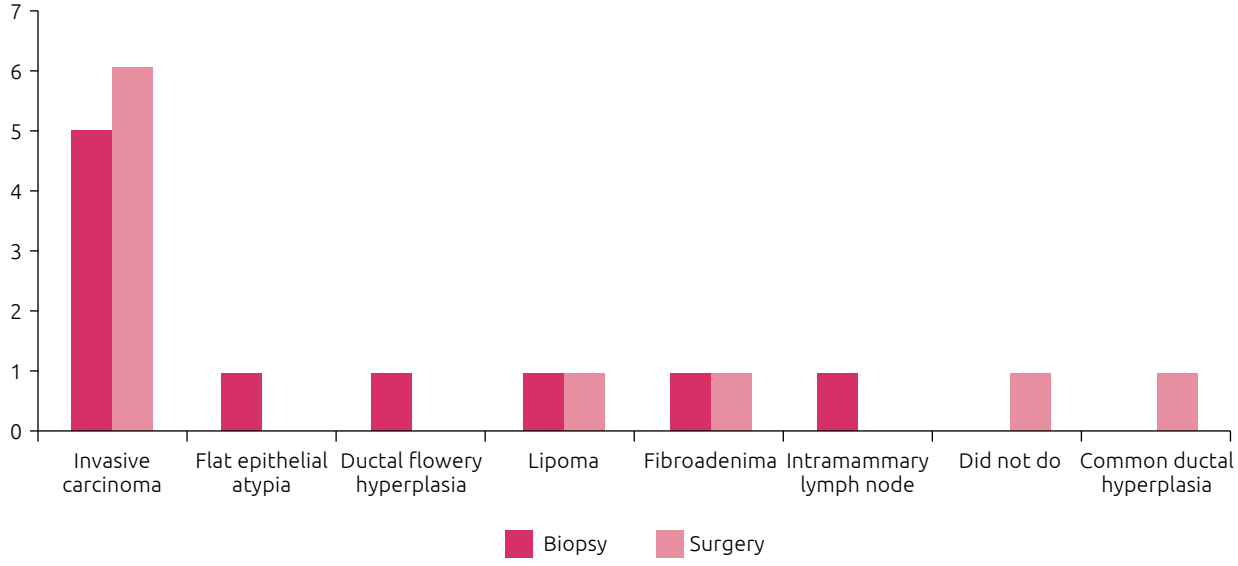

Figure 4. Histopathology of lesions classified as BIRADS® 4B.

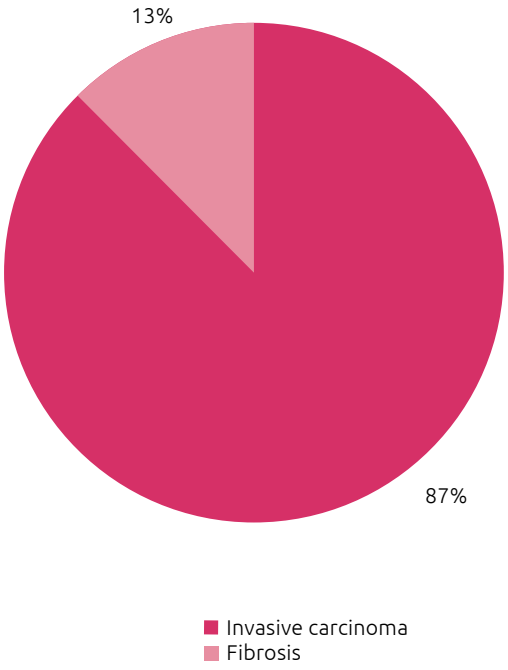

Figure 5. Histopathology of lesions classified as BIRADS® 5.

- Category 4A: low suspicion of malignancy;
- Category 4B: moderate suspicion of malignancy;
- Category 4C: high suspicion of malignancy;
- Category 5: highly suggestive of malignancy and
- Category 6: malignancy proven by biopsy[4].

The malignancy estimate, according to BIRADS®, ranges from 2% for category 3 lesions up to 95% for those classified as category 5.

The results obtained in the research are close to those found in the literature and corroborate the behaviors already used in clinical practice. When the nodule presents ultrasound characteristics, such as regular margins, defined limits and absence of posterior acoustic shadow, the greater probability is that it is a benign lesion, which enables only one follow-up, thus avoiding costly and uncomfortable procedures to the patient.

However, the breast lesions cases with unfavorable ultrasound characteristics, which point to a greater probability of breast cancer diagnosis, require an energetic propaedeutic for a more efficient treatment.

The positive predictive value of category 5 reaches 100% in some studies[5]. A research found 100% agreement between the findings characterized as BIRADS® 5 and the anatomopathological result[6]. Onur et al. found a sensitivity and specificity of 93.5% and 100%, respectively, in core biopsy results, when correlated with mammographic BIRADS®[7].

The classification of BIRADS® 4A diagnoses a higher percentage of benign lesions, that is, less than 5% of malignancy. In the present study, benignity was identified in almost 100% of these patients, which brings us the questioning in the biopsy procedure in all these cases. However, the current conduct of BIRADS® does not allow us to omit biopsy in these cases. Some had incomplete sub-classification information, among which there were cases of breast carcinoma, not giving us certainty that this group of patients would benefit from clinical follow-up only.

In the present study, the fragment biopsy procedure in mammary lesions with a benign anatomopathological diagnosis, especially in those classified as BIRADS® 4 A, had a positive impact on the reduction of the surgical approach and a relevant implication in the reduction of costs in health services.

CONCLUSION

In conclusion, the ultrasound features of breast lesions have a high predictive value in the final diagnosis, mainly in nodules with benign characteristics in the image examination, which is a fundamental datum for the decision of conduct in an adequate time in each situation.

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ORIGINAL ARTICLE
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ALTERATION OF BONE MINERAL DENSITY IN BREAST CANCER FEMALE SURVIVORS ON CHEMOTHERAPY TREATMENT: AN INTEGRATIVE REVIEW

Alteração da densidade mineral óssea em mulheres sobreviventes de câncer de mama tratadas com quimioterapia: revisão integrativa da literatura

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ABSTRACT

Introduction: Chemotherapy for treatment of patients with breast cancer has increased the survival of this population. However, it can significantly reduce bone mineral density (BMD). **Objective:** To verify bone mineral density modifications in women with breast cancer undergoing chemotherapy, as well as their clinical characteristics and risk factors. **Methods:** Integrative review of papers published from 2006 to 2016, carried out through specific terms in PubMed and SciELO databases. **Results:** In that period, 898 papers were identified (897 in PubMed and 1 in SciELO). Among the six papers recovered, there was a considerable reduction in lumbar spine and femoral bone mass. For women submitted to chemotherapy, the main regimens associated with the reduction were doxorubicin and cyclophosphamide (AC), cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and cyclophosphamide, epirubicin and 5-fluorouracil (FEC). In addition, there was greater BMD reduction among women aged more than 50 years, Caucasian and who presented early ovarian failure induced by chemotherapy. **Conclusion:** The use of chemotherapy for breast cancer may lead to bone mass loss, especially when AC, CMF and FEC are used in women aged more than 50 years and among those with early menopause due to this treatment.

DESCRIPTORS: Breast neoplasms; Bone mineral density; Chemotherapy

RESUMO

Introdução: O uso de quimioterápicos para o tratamento de pacientes com câncer de mama tem aumentado a sobrevida dessa população. Entretanto, pode reduzir significativamente a densidade mineral óssea (DMO). **Objetivo:** Verificar a alteração da densidade mineral óssea em mulheres com câncer de mama submetidas a quimioterapia, assim como as características clínicas e os fatores de risco. **Métodos:** Revisão integrativa da literatura de artigos publicados no período de 2006 a 2016, realizada por meio de termos específicos nos bancos de dados da PubMed e da SciELO. **Resultados:** No período selecionado, foram identificados 898 artigos (897 na base PubMed e 1 na SciELO). Entre os seis artigos recuperados para leitura na íntegra, observou-se redução considerável na massa óssea na coluna lombar e no fêmur. Os principais tipos associados à redução foram os regimes doxorrubicina e ciclofosfamida (AC), ciclofosfamida, metotrexato e 5-fluorouracil (CMF) e ciclofosfamida, epirrubicina e 5-fluorouracil (FEC). Além disso, houve maior redução da DMO entre as mulheres com idade acima de 50 anos, caucasianas e que apresentaram falência ovariana precoce induzida pela quimioterapia. **Conclusão:** O uso de quimioterápicos para tratamento do câncer de mama pode acarretar perda de massa óssea, principalmente quando se utilizam os regimes AC, CMF e FEC em mulheres com idade acima de 50 anos e entre aquelas que apresentam menopausa precoce decorrente desse tratamento.

DESCRITORES: Neoplasias da mama; Densidade mineral óssea; Quimioterapia

Study carried out at the Advanced Center for Breast Diagnosis (CORA), *Hospital das Clínicas* (HC)/*Universidade Federal de Goiás* (UFG) – Goiânia (GO), Brazil.
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INTRODUCTION

Breast cancer is an important neoplasm that affects women all over the world. Chemotherapy (CT) is still one of the main types of treatment recommended to most of the women with a located disease, thus providing a recurrence reduction of around 30% and an increase of patients' survival[1]. However, this systemic treatment may include several side effects, such as modification of body composition with increase of total and abdominal body fat and loss of muscle mass; decrease of bone mineral density (BMD), which can result or intensify a preexisting condition of osteopenia and osteoporosis; and induction of premature ovarian failure (POF) in the pre-menopause period, among other comorbidities[1-3].

Regarding BMD damage, osteoporosis is characterized by the loss and deterioration of bone mass associated with the reduction of serum estrogen concentration with later deterioration of its microarchitecture and predisposal to risk of falls, injuries and fractures[4], with higher prevalence in Caucasian women[5].

Estrogen failure after menopause leads to misbalance of bone reabsorption and formation, and the increase of bone reabsorption exceeds that of formation[6]. This misbalance contributes to loss of bone quality, which increases the incidence of osteoporosis[7].

The decrease of estrogen endogenous production throughout the menopause transition has been associated with loss of BMD and skeleton muscle mass. In addition, aging per se promotes body composition modifications that result in a pattern of central fat accumulation or android distribution[8].

It is possible that CT causes damage to the female gonads, and the extent and/or evolution of this damage depends on the drug, prescribed dose, treatment period, and patient's age. Around 70% of the women develop POF associated with BMD decrease in the femoral shaft and lumbar spine[3]. Women whose menstrual cycle is not affected do not present significant bone loss; however, these cases are rare[9]. Postmenopausal women, on the other hand, have the protective role of body mass in the skeleton, especially regarding the risk of fractures and loss of bone mass during and immediately after menopause[10].

In recognizing the risk of CT treatment to bone health and its consequences to the quality of life of these patients, the aim of this study was to verify the BMD modification of breast cancer women who underwent CT, as well as the clinical characteristics and risk factors for low BMD.

METHODS

This is an integrative literature review of retrospective or prospective studies and clinical trials published in the last 10 years. The collection was carried out in September 2016, using primary and secondary search strategies in PubMed and SciELO computed databases.

The limits used for the bibliographic research were articles published between 2006 and 2016 in English and Portuguese, regarding humans and female sex.

The indexation terms for study collection were: breast cancer [Mesh], bone mineral density [Mesh] and chemotherapy [Mesh], which were used in combination and were based on Boolean operators.

The articles were evaluated following the inclusion and exclusion criteria illustrated in Chart 1.

Then, the texts were read in full and analyzed following the script that considered characteristics of the study (research type and outline, year and place of conduction, follow-up period, evaluation methods), participants (number of participants, inclusion criteria, age range, and anthropometric data), and the main clinical outcomes (Figure 1).

RESULTS

Eight hundred and ninety eight papers were identified (897 in PubMed base and 1 in SciELO base). After careful reading, six studies met all the inclusion criteria (Chart 1). The chosen papers were included in Table 1 in order to better describe and compare the different results obtained by the authors. Other documents were also mentioned throughout this review as the theoretical basis and discussion of the theme. Studies that showed BMD modification based on the CT regimen are found in Table 2.

The present review gathered data of 468 women with breast cancer at stages I–III that had been previously chosen in five different countries: Germany[11], Turkey[12], China[13], England[14], and the United States[15,16]. The follow-up duration in all studies comprised at least 12 months.

Chart 1. Inclusion and exclusion criteria for the literature review.

Inclusion criteria	Prospective, retrospective studies published in PubMed and SciELO databases between 2006 and 2016. English and Portuguese languages. Female breast cancer survivors treated with chemotherapy, aged ≥18 years in pre and postmenopausal periods. To analyze anthropometric data (weight, height) and measure densitometry (BMD) after CT treatment.
Exclusion criteria	Drug interventions (use of corticosteroids, vitamin supplements, biphosphates). Presence of diabetic intervention and physical exercises. Women who had been previously treated for other kind of cancer and/or metastatic women. Experiments with animals, in men and *in vitro*. Case reports, opinions, reviews, abstracts, editorials.

BMD: bone mineral density; CT: chemotherapy.

Demographic and physical characteristics were obtained from structured interviews. Anatomopathological data were collected through the review of medical records. Some studies used evaluation of bone function serum markers, such as:

- osteoprotegerin (OPG), procollagen type 1 amino-terminal propeptide (P1NP), collagen type 1 c-terminal telopeptides (CTx); and
- Bone alkaline phosphatase (BAF).

All the studies analyzed the BMD before and after CT through the Dual-Energy X-Ray Absorptiometry (DXA), which is the gold standard for such purpose.

All studies with a control group presented samples divided into age, menopause status (as well as period of menopause), number of children, and body mass index (BMI).

Only two studies did not specify the kind of CT used[15,16]. The other papers found a significant reduction of the BMD in the lumbar spine, femoral shaft, and hip after the use of six cycles of doxorubicin and cyclophosphamide (AC)[11] and cyclophosphamide, epirubicin and 5-fluorouracil (FEC), with the onset of osteoporosis in patients aged more than 50 years[12]. It is worth noting that the studies were carried out in European countries, in the United States and in China, with high prevalence of Caucasian and postmenopausal women[11-16].

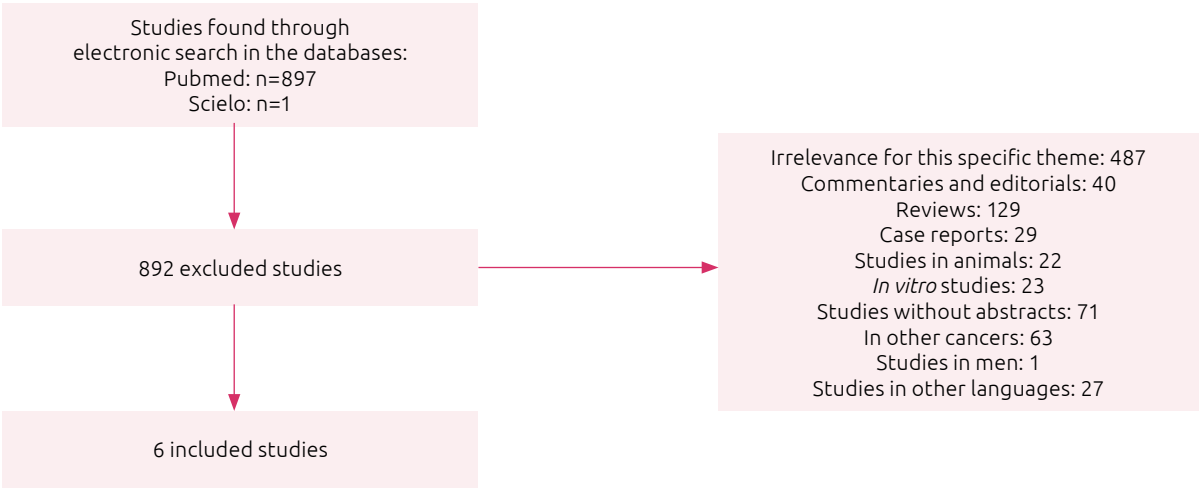

Figure 1. Flowchart of the study selection process, 2016.

Table 1. Selected articles.

Author, year, place	Population (n)	Study period	Study type	Mean age	Cancer staging
Hadji et al., 2009; Germany[11]	53 cases	12 months	Case-control	Cases 37.0 years old	I –III
	53 controls			Controls 38 years old	
Turan et al., 2009; Turkey[12]	26 cases	24 months	Case-control	Cases 49.0 years old	I–2
	21 controls			Controls 53.5 years old	II–19
					III–5
Loo et al. 2010; China[13]	120 cases	2001–2008	Case-control	66.9 years-old	I–11%
	118 controls				II–66%
					III–33%
Cameron et al., 2010; England[14]	41	2001–2003	Cohort	41.0 years-old	NR
Oostra et al.,2015; USA[15]	40	12 months	Cohort	42.0 years-old	I–II
Tabatabai et al., 2016; USA[16]	188	2006–2010	Randomized and controlled	45.9 years-old	NR

NR: non-reported.

Table 2. Modifications of the bone mineral density according to the chemotherapy regimen.

Author, year, place	CT regimen	BMD g/cm²	Δ	p-value	BMI kg/m²	Methods – interventions	Main outcomes
Hadji et al., 2009; Germany[11]	AC	NR	NR	<.0010	Control±25.0	Serum dosage: bone turnover markers; BMD through the DXA: lumbar spine, femoral shaft, and hip	Levels of bone markers increased as the BMD decreased
					Cases±25.0		In the case group, osteopenia increased from 23.5 to 39.2% after 12 months of CT
Turan et al., 2009; Turkey[12]	FEC	Mean of lumbar spine cases: 0.9380	NR	=0.010	Cases ±28.1 Controls ±28.5	BMD through DXA: lumbar spine, femoral shaft, trochanter and Ward's triangle	The spine BMD was lower in the case group (p=0.01);
		Mean of lumbar spine controls: 1.0660					The OP was higher in patients <50 years old during the CT
Loo et al. 2010; China[13]	CMF	Means of cases: mandible:	0.290	<0.050	NR	Serum dosage: hormones (estradiol, progesterone, luteinizing hormone, FSH), minerals (calcium, phosphate and magnesium) and bone turnover markers; BMD through the DXA: mandible and left hip	Menopause was marked by estrogen failure, which was more seen in the first 5 years in the G1 Patients receiving CT had a decrease of the mandible BMD in the left hip
		before CT: 1.11					
		After 48 months of CT: 0.87					
		After 60 months of CT: 0.82					
		Mean of controls: mandible	0.170				
		before CT: 1.28					
		After 48 months of CT: 1.15					
		After 60 months of CT: 1.11					
		Mean of cases: left hip	0.271				
		before CT: 0.8080					
		After 48 months of CT: 0.5912					
		After 60 months of CT: 0.5370					
		Mean of controls: left hip	0.172				
		before CT: 0.8510					
		After 48 months of CT: 0.7134					
		After 60 months of CT: 0.6790					
Cameron et al., 2010; England[14]	3 CMF	Lumbar spine	0.050	<0.001	NR	Serum dosage: estrogen and FSH – bone turnover markers; BMD through the DXA: lumbar spine and hip	Decrease of BMD in the lumbar spine and hip in 6 and 12 months after CT (p<0.001); Increase of serum markers of bone turnover after 1 year of CT No significant relation between the levels of FSH and BMD
		before CT: 1.05					
		After 6 months of CT: 1.01					
	27 AC	After 12 months of CT: 1.00					
		Total hip					
	11 AT	before CT: 0.95					
		After 6 months of CT: 0.91					
		After 12 months of CT: 0.90					

Continue...

Tabela 2. Continuation.

Author, year, place	CT regimen	BMD g/cm²	Δ	p-value	BMI kg/m²	Methods – interventions	Main outcomes
Oostra et al.,2015; USA[15]	NR	NR	NR	NR	23	Serum dosage: FSH, ionized Ca+, osteocalcin and osteoprotegerin BMD through DXA: lumbar spine and femur	Multivariate statistical analysis with ovarian failure induced by CT decreased the BMD of the lumbar spine and femur, 6 and 12 m. Osteoprotegerin decreased after 6 m (without significance after 12 m). Osteocalcin increased after 6 and 12 m
Tabatabai et al., 2016; USA[16]	NR	NR	NR	NR	26.1±6.4	Serum dosage: FSH; DXA: hip, lumbar spine and femur	Bone loss in the femoral shaft and lumbar spine; Less than 20% of the women continued menstruating after CT; Amenorrhea was associated with decrease of the BMD, both in the femoral shaft and in the spine

CT: chemotherapy; BMD: bone mineral density; BMI: body mass index; AC: doxorubicin and cyclophosphamide; NR: non-reported; DXA: Dual-Energy X-Ray Absorptiometry; FEC: cyclophosphamide, epirubicin and 5-fluorouracil; OP: osteoporosis; POF: premature ovarian failure; CMF: cyclophosphamide, methotrexate and 5-fluorouracil; FSH: follicle-stimulating hormone; G1: case group (breast cancer patients); AT: anthracyclines and taxanes.

An investigation carried out in England evaluated the impact of CT in the BMD of three groups of postmenopausal women that used cyclophosphamide, methotrexate and 5-fluorouracil (CMF), followed by doxorubicin (A-CMF) or FEC, followed by docetaxel (FEC-T). There was no significant reduction of the lumbar spine and hip BMD regardless of age, BMI, estradiol levels, and CT regimen. When the group of women presenting with amenorrhea was compared with those that did not develop it, the authors found a significant decrease of the BMD in the first group ($p<0.001$)[14].

A study assessed the quality of life of 26 Turkish women with breast cancer who underwent six cycles of CT (CMF). The authors used the SF-36 questionnaire as an instrument. Postmenopausal women showed worse quality of life compared with the control group due to the higher physical limitation in daily activities. There were no alterations in the mental domain; however, the pain score had mean of 70.8 (±32.7), considering the patients presented osteoporosis and osteopenia[12].

DISCUSSION

CT seems to induce the reduction of BMD in the lumbar spine and femoral shaft segments, the decrease of femoral cortical porosity, and the decrease of femoral bone endurance, thus increasing the risk of fractures[14]. In studies reporting chemotherapeutical agents, the most vulnerable groups were those receiving treatments with AC, CMF and FEC, women aged more than 50 years and who developed POF[11-14]. Furthermore, these chemotherapeutical agents are myotoxic to musculoskeletal, which leads to dose-dependent myofibrillar loss.

This alteration is possibly associated with the action of alkylates originated from the CT that cause gonadal toxicity, which is commonly associated with the POF. The alterations seen in the bone mass, according to different studies, are influenced by the patient's age, type, dose of chemotherapeutical agent, and treatment period. These factors are found interconnected; therefore, they influence concomitantly the loss of bone mass[17]. The loss of cortical bone mass is related to estrogen failure, which contributes to age-related bone loss[18].

There is a relation between chemotherapy treatment, POF in pre-menopause, weight gain and bone mass loss due to the reduction of estrogens[11]. This effect seems to have a direct correlation with the chemotherapeutical agent dose, in addition to damaging vascularization and ovarian stroma, which, regardless of the loss of oocytes and cells of

granulosa, are related to the gonadotoxic effect of CT. The authors pointed out that ovarian aging after CT seems to develop due to a series of factors, such as apoptosis, alterations in the DNA of oocytes and in the granulosa cells, as well as vascular changes[11].

Women with osteoporosis diagnosed before the diagnosis of breast cancer, who underwent CT treatment, present an expressive risk of intensifying bone loss due to the toxic action of CT, regardless of their menopausal status. Furthermore, the risk is even higher among pre-menopausal women due to POF[9]. On the other hand, a reduction in breast cancer incidence in women with POF is known, when compared with those in the menopause at a habitual age (OR=0.59; 95%CI 0.38–0.91)[19].

A cohort study with North-American patients in the premenopausal period aged around 45.9 years aimed to assess the relationship between the level of follicle-stimulating hormone (FSH) in the baseline and the BMD modification after CT treatment. After the regression analysis adjusted by age, ethnicity, physical activity practice, initial BMD and quantity of C-reactive protein, the authors found that the lowest levels of FSH were associated with bone loss in the lumbar and femoral shaft segments after 12 months of follow-up ($p<0.001$). Amenorrhea was also associated with decreasing BMD in both evaluated sites[16], which does not occur in breast cancer patients whose neoplasm cells present positive estrogen receptors, and the absence of menstrual flow – if early diagnosed – may determine better prognosis[20].

A cohort research carried out with 40 American women in the premenopausal period aiming at evaluating the relation between OPG and bone loss in women with CT-induced POF found a reduction of the BMD in the lumbar spine and femoral shaft when they were evaluated 6 and 12 months after the beginning of the systemic treatment ($p<0.001$). The authors found a suppression of the ovarian function in both assessed periods, whereas the OPG was significantly high only in the first six months. The authors pointed out that such increase would be a compensatory attempt of the organism to stop the quick bone loss during the treatment, considering that the OPG has an inhibitory activity on the osteoclasts[15].

In addition, women with cancer and hypergonadotropic amenorrhea show a significant reduction of the bone mineral mass in the lumbar spine compared with the hypogonadotropic women; therefore, the negative correlation between the levels of FSH and BMD in this anatomical site calls our attention, which signalizes the follicle reserve depletion. This may also be explained by the fact that the lumbar spine has a larger surface and is more metabolically active; thus, it is more prone to mineral balance modifications[15].

The estrogen level required to maintain a relative regular bone remodeling in postmenopausal women is lower than that required to stimulate the classical target tissues, such as those of breast and uterus. Furthermore, the risk of fractures is inversely related to the levels of estrogen in the postmenopausal period, and one fourth of the estrogen dose, which would stimulate uterus and breast, would be sufficient to decrease bone reabsorption and increase bone mass in elderly women[21].

The BMI effects on fractures at a certain level of the BMD remain controversial due to the different effects on several fracture locations. In a cross-sectional study including 48 women with mammary neoplasms, a high percentage of body fat was verified in all the patients in the android area obtained through the DXA[22]. After analyzing the association between the risk of fractures and the BMI in healthy women aged around 63 years, a recent meta-analysis showed that the hazard ratio (HR) for osteoporotic fractures was 0.87 (0.85–0.90), when a BMI of 25 kg/m^2 was under analysis. However, when it was adjusted for the BMD, the same analysis showed an increase of the HR for osteoporotic fractures (HR=1.16; 95%CI 1.09–1.23). This investigation included prospective studies conducted in more than 25 countries. Obesity (BMI≥30 kg/m^2) was present in 22% of these subjects, and there were 30,280 osteoporotic fractures in the follow-up period. The authors concluded that the association between BMI and fractures is complex, different between the skeletal sites and modified due to the interaction between the BMI and the BMD[23].

The studies developed to assess the relationship between BMD and CT in breast cancer both agree to attribute the worst clinical outcome to CT. However, based on the populations and designs of different studies, most of these papers are observational and sometimes have conflicting results.

In association with the development of bisphosphonate, of the estrogen receptor selective modulators and vitamin D supplementation, the early identification of the high risk presented by the breast cancer population of having osteoporotic fractures is considered an effective strategy to reduce this condition. Hence, substantial efforts have been made to identify clinical risk factors, in addition to the BMD, and to integrate them to risk assessment tools or to predicting models, such as the Fracture Risk Assessment Tool (FRAX) and the Garvan Fracture Risk Calculator. In addition, vitamin D has been used in cancer patients due to its effect on the prevention of growth of tumor cells possibly reducing tumor metastases[24]. New studies establishing such relation should be carried out, especially regarding bone metastasis.

Besides the aspects directly related with the decrease of BMD and health risks, this alteration can directly affect the patients' perception of their quality of life. We also found, among breast cancer women treated with CT, that those presenting a reduction of the BMD had a worse evaluation of quality of life, especially in the physical functionality aspect[12].

Therefore, in the light of current knowledge on mammary neoplasm follow-up protocol, the following should be included: incentive to food reeducation and physical exercises, to proper vitamin supplementation, to bone mass monitoring, and to customized multidisciplinary service in order to promote early therapeutic intervention and improve the quality and survival of these patients in the pre and postmenopausal periods.

CONCLUSION

We found that CT might have different influences on the BMD of breast cancer patients, with significant reductions in the lumbar spine and femoral shaft, which can lead to the increase of fracture risk and worse quality of life perception. In addition, the main regimens associated with decrease of BMD were AC, CMF and FEC, especially in women aged more than 50 years and with POF.

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ASSESSMENT OF FEMALE SEXUAL FUNCTION AND QUALITY OF LIFE AMONG BREAST CANCER SURVIVORS WHO UNDERWENT HORMONE THERAPY

Avaliação da função sexual e da qualidade de vida de mulheres sobreviventes do câncer de mama submetidas a hormonioterapia

Ana Beatriz Gomes de Souza Pegorare[1]*, Keslyn da Rosa Silveira[1], Ana Paula Simões No[1], Susi Rosa Miziara Barbosa[1]

ABSTRACT

Objective: The aim of this study was to investigate the sexual function and quality of life of breast cancer survival women. **Methods:** This is a cross-sectional study including 36 women who underwent breast cancer surgery (17 mastectomies and 19 quadrantectomies), sexually active, undergoing hormone therapy, aged 37 to 60 years old. Data were collected through the Female Sexual Function Index (FSFI) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). **Results:** In this study, 61.1% of the women had sexual dysfunction. Regarding quality of life, younger women were more impacted in their functional capacity (p=0,049). **Conclusion:** The prevalence of sexual dysfunction is higher in breast cancer survival women, with hypoactive desire and dyspareunia. Regarding quality of life, greater impairment of functional capacity was observed in young women.

KEYWORDS: Breast cancer; quality of life; sexuality; mastectomy.

RESUMO

Objetivo: O intuito deste trabalho foi investigar a função sexual e a qualidade de vida das mulheres sobreviventes do câncer de mama. **Métodos:** Trata-se de um estudo de corte transversal, incluindo 36 mulheres submetidas à cirurgia de câncer de mama (17 mastectomias e 19 quadrantectomias), sexualmente ativas, em tratamento hormonioterápico, com idade entre 37 e 60 anos. O instrumento utilizado para avaliar a função sexual foi o *Female Sexual Function Index* (FSFI) e, para a qualidade de vida, o *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire* (EORTC QLQ-C30). **Resultados:** Neste estudo, 61,1% das mulheres apresentaram disfunção sexual. Em relação à qualidade de vida, mulheres mais jovens foram mais impactadas em sua capacidade funcional (p=0,049). **Conclusão:** A prevalência de disfunção sexual é elevada nas mulheres sobreviventes do câncer de mama, destacando-se o desejo hipoativo e a dispareunia. Em relação à qualidade de vida, foi observado mais prejuízo da capacidade funcional nas mulheres jovens.

PALAVRAS-CHAVE: Câncer de mama; qualidade de vida; sexualidade; mastectomia.

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INTRODUCTION

Breast cancer has a high incidence worldwide, being the second leading cause of cancer death in women. Approximately one in eight women over 35 years old will develop breast cancer during life. This fact makes the disease one of the most terrible among the female public[1-3].

Fortunately, advances in diagnosis and treatment have resulted in increased numbers of women surviving breast cancer. Consequently, it has led to disease-related research focusing on the analysis of quality of life, especially for female sexuality, which is a complex factor after cancer[4].

Most evidences show that women with cancer, in addition to changes in body function, suffer from fatigue and functional deficit in the upper limb homolateral to surgery. Also, due to the breast loss, women experience the feeling of not being physically attractive, generating low self-esteem and altered self-image, including on their own femininity, which can lead to depression[5]. In relation to sexuality, there are a variety of complaints. Dyspareunia, lack of vaginal lubrication, hypoactive desire and loss of breast tenderness have been reported as consequences of breast cancer treatment[6,7].

After the surgery (a physically and psychologically traumatizing experience), the women could be negatively affected in their sexuality. Therefore, this study aimed to investigate the sexual function of women surviving breast cancer, identifying possible factors that may interfere in the quality of patients who underwent modified radical mastectomy (MRM) or conservative surgery (CS) for breast cancer.

METHODS

This is a cross-sectional study, carried out at the Alfredo Abrão Cancer Hospital, located in Campo Grande, Mato Grosso do Sul, Brazil. The project was previously approved by the Research Ethics Committee of the Universidade Federal de Mato Grosso do Sul, under Protocol no. 44422915.70000.00.

The volunteers were recruited through a medical chart survey based on inclusion criteria and subsequent telephone contact, from January to November 2016. Prior to inclusion, they were clarified about the objectives, risks and benefits of the research, and those who wished to participate signed the Informed Consent Term (ICT), according to Resolution no. 466/2012.

Inclusion criteria were: age between 37 and 60 years old; fixed partner in the last six months; have undergone MRM or CS; and having been treated with adjuvant chemotherapy and radiation therapy using tamoxifen, for at least six months. The exclusion criteria were: cognitive impairment that made it impossible to understand the issues; illiteracy; sexual abstinence in the last six months; disease recurrence; metastasis; and breast reconstruction.

To collect data, three instruments were used: the first one was a form developed specifically for this research, which included sociodemographic data (age, occupation, marital status, religion and schooling) and personal background. The second instrument was the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[8]. The third instrument was the Female Sexual Function Index (FSFI)[9]. The last two questionnaires, in the public domain, were validated, translated and adapted to the Portuguese language. The EORTC QLQ-C30 was proposed by the European Organization for Research and Treatment of Cancer by Aaronson et al.[8], and validated and translated into Portuguese by Pais-Ribeiro et al.[10]. This questionnaire has the capacity to evaluate the quality of life of patients with cancer. It is composed of 30 questions, which are subdivided into three groups of scales:

1. The overall state of health and quality of life (QL2);
2. Functional scale, consisting of physical functioning (PF2), functional limitations (RF2), emotional functioning (EF), cognitive functioning (CF) and social functioning (SF);
3. The symptomatic scale, consisting of the subscales fatigue (FA), nausea and vomiting (NV), pain (PA), shortness of breath (DY), insomnia (SL), lack of appetite (AP), constipation diarrhea (DI) and financial difficulties (FI).

In this questionnaire, the scales follow the score ahead:

1. No;
2. Little;
3. Moderately;
4. Very.

With the exception of the global health scale, it consists of two questions that ask the patient to rate their general health and quality of life in the last week, using a score from 1 to 7, being: (1) very poor; and (7) great.

Scores are calculated separately for each scale, all ranging from 0 to 100. On the global health scale, the higher the score, the better the quality of life; for the functional scale, the higher the score, the better the function; and for the scale of symptoms, the higher the score, the worse the symptoms.

The FSFI questionnaire, constructed in the English language by Rosen et al.[9], was validated and translated into Portuguese by Thiel et al.[11]. The questionnaire is composed of 19 questions, which report on six domains of sexual response: desire and subjective stimulus; excitement; lubrication; orgasm; satisfaction; and pain or discomfort. Individual scores are obtained by summing the items that comprise each domain (simple score), which are multiplied by the factor of that domain and provide the weighted score. The final score (total score: minimum of 2 and maximum of 36) is obtained by the sum of the weighted scores of each domain. A total score lower than 26.5 is defined as sexual dysfunction[12].

Statistical analysis

The data were stored by the Microsoft Excel® program, for later analysis in the software SigmaPlot, version 12.5. The qualitative measures of the sample were described by absolute and relative percentage and frequencies; the quantitative ones, by mean and standard deviation. For the evaluation of linear correlation, the Spearman correlation was performed. The Mann-Whitney test was used when comparing the categorical variables (age, tamoxifen use and scores on the EORTC QLQ-C30 and FSFI scales). The significance level considered was 5%.

RESULTS

We evaluated 36 eutrophic, sedentary, postmenopausal women with a mean age of 52.03±1.07 years old (ranging from 37 to 60 years old), with active sexual life in the last six months, married (75%) or in a stable union (25%), 90% with at least one child, 75% of graduates in high school, 79% unemployed or a housewife, 55% with sufficient income for their expenses, 45% in the capital and 55% in the countryside of Mato Grosso do Sul. The mean age of the husbands/mates was 63.03±2.05 years old (ranging from 39 to 65 years old), 44% of them were high school graduates and 70% were employed at the time of evaluation. Regarding the type of breast cancer surgery, 47.2% (n=17) of the women had been submitted to MRM, and 52.8% (n=19) to the CS.

The clinical characteristics of the women evaluated are shown in Table 1. Women were classified into two groups according to the type of surgery, and analyzed regarding the variables: age, body mass index (BMI), period of tamoxifen use, and scores on EORTC QLQ-C30 and FSFI scales. Regarding these variables, there was no significant difference between mastectomized women and those ones who underwent CS.

Table 2 shows the results regarding the comparison between women who used tamoxifen for a period of up to three years and those who used the drug for more than three years, in relation to the variables age and scores on the EORTC QLQ-C30 and FSFI scales, including its scales and domains — it was observed that there was no significant difference in relation to these variables (Mann-Whitney test, p value varying between 0.154 and 0.986).

The results regarding the comparison between women aged 37 to 45 years old and those over 45 years old, in relation to the variables period of tamoxifen use and scores on the EORTC QLQ-C30 and FSFI scales, are presented in Table 3. In the analysis of the other variables, there was no significant difference.

In the analysis of quality of life (Figure 1), greater functional impairment was observed in young women (p<0.49) regardless of the type of surgery performed. Overall, 50.0% of the women reported incapacity to perform great efforts, 36.1% were worried, 33.3% were stressed, 30.5% were irritated, and 27.7% reported forgetting their memories or dates. In the analysis of symptoms, 41.6% of the women reported pain, and 27.7%, nausea (Table 4). In other questions, there was no significant percentage.

One study determined the cut grade to determine sexual dysfunction (SD) by means of the FSFI questionnaire, considering score ≤26,55[12]. Thus, SD was observed in women submitted to both surgeries, with no statistically significant difference between them (MRM=23.00±3.62 *versus* CS 20.58±1.51, p=0.472). Among the women evaluated, 66.60% presented some degree of SD, 73.68% of the women were submitted to CS, and 58.82% to MRM, according to the FSFI. The results are presented in Tables 3 and 5, including the scales, the domain and the questions that presented relevance in the study population.

In the "sexual desire" domain, the FSFI questionnaire classifies the first phase of the sexual response. A deficit at this stage results in hypoactive sexual desire disorders[13]. In this study, it was observed that 75% of the women never or few times felt sexual desire and 50% considered the degree of libido low.

Table 1. Results of the comparison between mastectomized and quadrantectomized women, regarding the variables age, period of tamoxifen use and scores in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and in the Female Sexual Function Index (FSFI).

Variable	Type of surgery		P value
	Mastectomy	Quadrantectomy	
Age	52,71±1,34	51,42±1,66	0,715
Period of tamoxifen (months)	26,88±3,89	33,90±4,18	0,200
EORTC QLQ-C30			
Global Health Scale	81,86±4,81	78,95±4,95	0,734
Functional scale	78,17±4,47	79,53±4,45	0,799
Symptom Scale	18,85±5,26	19,70±5,03	0,824
FSFI			
Desire and subjective stimulation	2,89±0,25	2,78±0,23	0,846
Excitement	3,00±0,40	2,98±0,28	0,738
Lubrication	3,65±0,47	3,79±0,41	0,812
Orgasm	3,72±0,48	3,71±0,36	0,726
Satisfaction	4,35±0,48	3,92±0,39	0,370
Pain or discomfort	3,55±0,44	3,77±0,43	0,799
Total score	21,17±2,20	20,94±1,81	0,704

Results are presented as mean±standard error of the mean. P value in the Mann-Whitney test.

The second phase of the sexual response is classified by FSFI in the "excitation" and "lubrication" domains, and includes physiological and subjective sexual arousal as a response to vaginal engorgement and vaginal lubrication. In this study, 36.1% of the participants classified their degree of sexual arousal as low or absent during activity or sexual intercourse. And 27.7% reported never or seldom achieving proper vaginal lubrication, and they had difficulty in maintaining lubrication during intercourse.

In the "orgasm" domain, the third phase of the female sexual response, the climax (or maximum point of sexual tension), rhythmic contractions of the genital muscles and intense subjective involvement are evaluated. Disorders in these factors provide alterations in female orgasm[13]. In this study, 44.4% of the women never or rarely reached orgasm and 36.1% had difficulty reaching it during the sexual act.

The final phase of the sexual response includes the physical relaxation of tension and subjective feeling of well-being. A disturbance at this stage may lead to pelvic pain and vaginismus[14]. In this area, the questionnaire covers questions about pain during

Table 2. Results of the comparison among women who used tamoxifen for three years and those who used the drug for a longer period, in relation to the variables age and scores in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and in the Female Sexual Function Index (FSFI).

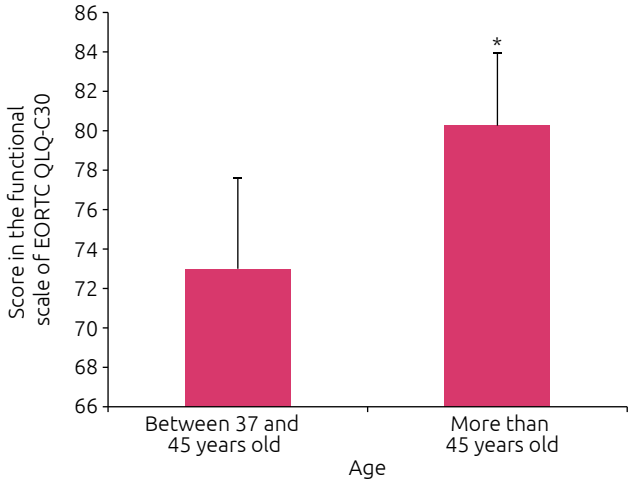
Variable	Period of tamoxifen use		P Value
	Up to 3 years	More than 3 years	
Age	51,92±1,22	52,30±2,28	0,873
EORTC QLQ-C30			
Global Health Scale	81,73±4,31	76,67±5,24	0,214
Functional scale	77,69±3,89	82,00±4,96	0,915
Symptom Scale	20,12±4,84	17,18±3,11	0,303
FSFI			
Desire and subjective stimulation	2,72±0,21	3,12±0,25	0,305
Excitement	2,80±0,30	3,48±0,34	0,347
Lubrication	3,76±0,39	3,63±0,44	0,658
Orgasm	3,49±0,36	4,28±0,45	0,312
Satisfaction	3,89±0,38	4,72±0,45	0,154
Pain or discomfort	3,61±0,39	3,80±0,46	0,986
Total score	20,29±1,77	23,03±1,97	0,572

Results are presented as mean±standard error of the mean. P value in the Mann-Whitney test.

Table 3. Results of the comparison among women aged between 37 and 45 years ols and those ones over 45 years old, regarding the variables period of tamoxifen use and scores in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and in the Female Sexual Function Index (FSFI).

Variable	Age		P Value
	Between 37 and 45 years	More than 45 years	
Tamoxifen use (months)	31,00±7,74	30,48±3,14	0,903
EORTC QLQ-C30			
Global Health Scale	73,81±8,02	81,90±3,79	0,178
Functional scale	73,02±4,64	80,31±3,68	0,049
Symptom Scale	19,41±8,93	19,27±3,98	0,857
FSFI			
Desire and subjective stimulation	2,91±0,38	2,81±0,19	0,699
Excitement	3,56±0,65	2,86±0,25	0,138
Lubrication	3,73±0,74	3,72±0,34	0,952
Orgasm	4,11±0,73	3,61±0,32	0,399
Satisfaction	4,97±0,59	3,92±0,34	0,086
Pain or discomfort	3,71±0,81	3,66±0,33	0,904
Total score	23,00±3,62	20,58±1,51	0,472

Results are presented as mean±standard error of the mean. P value in the Mann-Whitney test.



*Significant difference in relation to the group and women aged between 37 and 45 years old (Mann-Whitney test, p=0.049).

Figure 1. Score in the functional scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), among women aged between 37 and 45 years old and those ones over 45 years old. Each column represents the mean; the bar indicates the standard error of the mean.

Table 4. Characteristics of the women obtained by questionnaires in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and in the Female Sexual Function Index (FSFI).

	Type of Surgery		%
	Mastectomy	Conservative surgery	
EORTC QLQ-C30			
Functional Scale			
Great effort	9	9	50.00
Concerned	8	5	36.11
Stressed	5	7	33.33
Irritated	5	6	30.55
Forgetfulness	3	7	27.77
Symptom Scale			
Pain	6	9	41.66
Nausea	6	4	27.77
FSFI			
Desire and subjective stimulation			
Frequency of sexual desire	13	14	75.00
Degree of sexual desire	11	7	50.00
Excitement			
Degree of sexual excitement	6	7	36.13
Lubrication			
Vaginal lubrication	5	9	38.88
Difficulty to lubricate	2	8	27.77
Maintaining lubrication-frequency	5	9	38.88
Difficulty to maintain lubrication	7	6	36.11
Orgasm			
Having an orgasm	7	9	44.44
Difficulty to have an orgasm	7	6	36.11
Pain or discomfort			
Pain during penetration	5	7	33.33
Pain after penetration	5	6	30.50

Results are presented as mean±standard error of the mean. P value in the Mann-Whitney test.

and after penetration, showing that 60.5% of women report discomfort always or most of the time.

DISCUSSION

Biopsychosocial problems associated with the diagnosis or treatment of cancer are complicated by the surgical removal of part or all of the breast. Breast loss is usually associated with problems and difficulties such as depression, affective disorders, loss of sexual interest, negative self-image, loss of femininity, and difficulties with clothing. These problems may persist for years after the treatment of breast cancer[15].

In the present study, 61.1% of women who survived breast cancer had SD. This number was well above those ones found by studies evaluating healthy women. A national study, with a sample of 1,219 women over the age of 18, showed that the prevalence of SD was 49%[16]. Another study, conducted in the State of Pernambuco, evaluated the prevalence of SD in women during the climacteric period, demonstrating a predominance of 46.2%[17].

In the present study, the occurrence of SD was elevated in women submitted to both surgical procedures, 68.4% of the women submitted to CS, and 52.9% of the mastectomized women. Corroborating this finding, a study that evaluated

Table 5. Results of the evaluation of the linear correlation between the period of tamoxifen use and age, with scores in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and in the Female Sexual Function Index (FSFI).

Variable	Variable	
	Period of tamoxifen use	Age
EORTC QLQ-C30		
Global Health Scale	p=0,471; r=-0,123	p=0,810; r=0,041
Functional scale	p=0,852; r=-0,032	p=0,314; r=0,172
Symptom Scale	p=0,302; r=0,176	p=0,581; r=0,094
FSFI		
Desire and subjective stimulation	p=0,317; r=0,171	p=0,659; r=-0,076
Excitement	p=0,459; r=0,127	p=0,505; r=-0,114
Lubrication	p=0,706; r=0,065	p=0,415; r=0,140
Orgasm	p=0,090; r=0,286	p=0,846; r=0,033
Satisfaction	p=0,252; r=0,195	p=0,854; r=-0,031
Pain or discomfort	p=0,611; r=0,087	p=0,696; r=0,067
Total score	p=0,303; r=0,176	p=0,713; r=0,063

p: p value in the Spearman linear correlation test; r: linear correlation coefficient.

sexual function after breast cancer found that the type of surgical procedure (MRM and CS) did not interfere with sexual function[18]. However, some studies have shown that women who underwent CS reported less impact on their sex lives and fewer concerns about sexual attraction than women who had MRM[6], revealing a high prevalence of SD in mastectomized women[19,20].

One limitation of this study is the sample size, which was limited because many of the women contacted did not have an active sex life. However, the first meta-analysis in the literature on SD in cancer patients admitted as an inclusion criterion clinical research with a sample of at least 30 cancer survivors. This number is considered adequate, thus limiting the heterogeneity, characteristic of studies with few participants[21].

SD is highly prevalent in women after breast cancer. In the present study, the participants presented problems related to sexual desire, excitement, reduction of sexual pleasure, difficulty in reaching orgasm, pain during and after the sexual act, factors that make sex less pleasurable.

The most frequent complaints were hypoactive desire and pain during intercourse, present in 75.0 and 60.5% of the women, respectively. In healthy women, complaints about hypoactive desire and pain in sexual intercourse are much less frequent, around 43.0 and 36.8%, respectively[22]. With chemotherapy-induced menopause, side effects such as pain or discomfort during intercourse are common, due to lack of lubrication during penetration and during sexual intercourse[23,24].

In the present study, 47.2% of the women were mastectomized and 52.8% underwent CS. There was no significant statistical difference between the types of surgery in the quality of life analysis (global health, functional capacity or symptoms), by the EORTC QLQ-C30 questionnaire.

The relationship between the type of surgery and aspects associated with the quality of life of women with cancer presents conflicting results. Some authors report that women submitted to CS reported better quality of life than those ones who underwent MRM[25,26], while others described a better psychological adjustment among those ones submitted to MRM[27,28] despite observing similar quality of life results[29,30]. The conflicting results can be explained by some methodological differences. They differ in the studied sample, in the design and in the research instruments, besides being influenced by cultural differences. Some authors applied generic (Medical Outcomes Study 36 — SF-36) and specific (EORTC QLQ-30) questionnaires.

However, a study of literary revision proposed by Kiebert et al. reports that the types of surgical procedures do not interfere in the social aspect of the quality of life, but differ in relation to the body image[31].

In the present study, it was observed that younger women presented greater functional impairment when compared to older women (>45 years). The functional scale of the questionnaire used (EORTC QLQ-C30) evaluates the difficulty that women report when performing effort, walking, reading, watching TV, washing, dressing, and participating in social and family activities[8].

A study with cancer survivors found a decrease in muscle strength and range of motion (for abduction, flexion, and lateral rotation of the shoulder homolateral to surgery), as well as impairment of functional capacity assessed by the SF-36 questionnaire[32]. Demonstrating that, regardless of the type of surgery (conservative or radical), there is significant functional limitation especially in what involves tasks such as washing clothes, washing dishes, carrying objects, driving and preparing food. This may be due to tissue damage, surgical manipulation, or even the feeling of protecting the upper limb, avoiding possible complications[33].

It is speculated a higher prevalence of functional impairment in young women. An explanation for this influence is justified since the young woman realizes more about the impact of cancer treatment due to her being more socially active and having more functional independence with regard to driving, carrying objects and preparing food, than an elderly woman[34].

In addition, it is important to emphasize the importance given by these women to the breast as a symbol of femininity, sexuality, maternity and body image[34].

Unlike the present study, Dialla et al. reported that older women present more fatigue, functional losses and muscle weakness associated with symptoms such as emotional instability, loneliness, mental fragility and lack of social support when compared to young women[36].

However, the women of the present study classified, in their majority (88.8%), global health in a positive way. It shows that there are other variables that can affect the quality of life, such as personality, culture, support of the spouse and family, religious or spiritual aspects, among others[37]. In the present study, age, period of tamoxifen use, and type of surgery were not determinants of sexual function and quality of life. It should be emphasized that problems related to sexual function should be taken to the multidisciplinary team, in order to promote health education, and provide medical, psychological and physiotherapeutic support to patients. It is of great importance that the sexual life of cancer survivors is not ignored by the team, and taboos concerning sexuality should be broken in the communication between the woman and the health professional, including such matters as bodily changes, breast loss, age, libido, among others.

CONCLUSION

It is concluded that the prevalence of sexual dysfunction is high in women survivors of breast cancer, regardless of the type of surgical procedure performed. Regarding quality of life, functional capacity impairment was observed in young women.

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PAGET'S DISEASE OF THE BREAST: STUDY OF CASES SERIES

Doença de Paget na mama: estudo de uma série de casos

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ABSTRACT

Objective: To evaluate the survival of a series of patients with Paget's disease of the breast. **Methods:** Observational, retrospective and descriptive study. Data were collected through electronic medical records; the following variables were obtained: age, tumor histology, tumor size, degree of differentiation, lymphatic invasion, vascular invasion, neural invasion, presence or not of potential involvement of axillary lymph nodes, immunohistochemical profile, treatments performed, recurrence, and follow-up. **Results:** Of the 301 cases of assisted breast cancer, six patients were identified with Paget's disease of the breast. The overall survival, with a mean follow-up of 54 months, was 100%. All individuals are free of disease activity. The most common histochemical profile was negative for estrogen and progesterone receptors, and positive for HER-2/neu. Axillary and/or distal metastatic involvement was not identified. **Conclusions:** Overall survival was 100%, with a mean follow-up of 54 months. This high rate is due to the absence of axillary and/or distal metastatic involvement in our series.

KEYWORDS: Paget's disease, mammary; breast; breast diseases; breast neoplasms; eczema.

RESUMO

Objetivos: Avaliar a sobrevida de uma série de pacientes com doença de Paget na mama. **Métodos:** Estudo observacional, retrospectivo, descritivo. Foram coletados os dados através de prontuário eletrônico e obtidas as seguintes variáveis: idade, histologia do tumor, tamanho do tumor, grau de diferenciação, invasão linfática, invasão vascular, invasão neural, presença ou não de comprometimento de linfonodos axilares, perfil imunoistoquímico, tratamentos realizados, recidiva e seguimento. **Resultados:** Dos 301 casos de câncer de mama atendidos, foram identificadas 6 pacientes com doença de Paget na mama. A sobrevida global, com um seguimento médio de 54 meses, foi de 100%. Todas estão sem doença em atividade. O perfil histoquímico mais frequente foi negativo para receptores de estrógeno e de progesterona, e positivo para o HER-2/neu. Não foi identificado comprometimento metastático axilar e/ou a distância. **Conclusões:** A sobrevida global foi de 100%, com um seguimento médio de 54 meses. Essa alta taxa deve-se à ausência de comprometimento metastático axilar e/ou a distância em nossa série.

PALAVRAS-CHAVE: Doença de Paget mamária; mama; doenças mamárias; neoplasias da mama; eczema.

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INTRODUCTION

Sir James Paget, a British surgeon and physiologist, was the first person to describe Paget's disease in 1874. Paget's disease of the breast (PDB) is a rare condition occurred exclusively in the papillary-areolar complex, usually associated with an underlying carcinoma and represents only from 0.5 to 5.0% of breast cancer cases[1-3]. The differential diagnosis includes chronic eczema, intraduct papilloma, basal cell carcinoma, apocrine carcinoma, melanoma, lymphoma, syphilitic cancer, erosive nipple adenomatosis, Bowen's disease of the skin, and ectasia of the breast duct[4].

The objective of the present study was to evaluate a series of patients with PDB.

METHODS

Observational, retrospective and descriptive study involving all women with PDB who attended a clinic in Teresina, Piauí, between 2001 and 2016. The data were collected by using electronic medical records and obtained the following variables: age, tumor histology, tumor size, degree of differentiation, lymphatic invasion, vascular invasion, neural invasion, presence or not of axillary lymph node involvement, immunohistochemical profile, treatments, recurrence, and follow-up.

The information collected was tabulated and analyzed by using the Microsoft Office Excel®, version 2007 (Microsoft, USA). Clinical staging was performed according to the TNM system of the American Joint Committee of Cancers (AJCC). Values of Ki-67≥13.9% were used as reference.

The study was approved by the Research Ethics Committee of *Universidade Federal do Piauí* (UFPI), No. 0354.0.045.000-11.

RESULTS

Of the 301 cases of breast cancer seen in the period, six patients were identified with PDB (Figure 1), determining a prevalence of 1,9%. The mean age of patients was 59 years old, ranging from 40 to 78.

In situ ductal carcinoma occurred in four cases; infiltrating ductal and lobular carcinomas in situ occurred, each one, in one case — tumors had a mean size of 1.8 cm. Of the six cases of PDB, 66.7% had high differentiation level; 16.7%, moderate differentiation level; and 16.7% were not classified in the histopathological report (Figure 2).

An assessment of the axillary lymph node condition was carried out in five patients. Among them, one underwent radical axillary emptying, in which 16 lymph nodes were evaluated, all of which were negative; four patients underwent research for sentinel lymph nodes, and all results were negative.

Four patients underwent a simple mastectomy and a segmental resection. In one case, the PDB manifested itself eight years after a mastectomy with preservation of skin and papillary-areolar complex (PAC), so that after the diagnosis of PDB, a resection of PAC was performed with free margins and preservation of both the prosthesis and the skin. A patient underwent chemotherapy and one, radiotherapy along with a conservative treatment. As for hormone therapy, a patient who presented positive estrogen receptor received adjuvant tamoxifen. The evolution of patients is shown in Table 1.

Regarding the analyzed molecular markers— HER-2/neu, proliferative index (Ki-67), estrogen receptor (ER), and progesterone receptor (PR) —, Table 2 was obtained (Figure 3).

One patient missed out on the follow-up. There were no deaths related to the disease. All subjects are alive and disease-free, with a mean follow-up of 54 months, ranging from 5 to 104 months since the breast cancer diagnosis.

DISCUSSION

The mean age of patients (from 59 years of age, ranging from 40 to 78) is in agreement with the literature, in which there

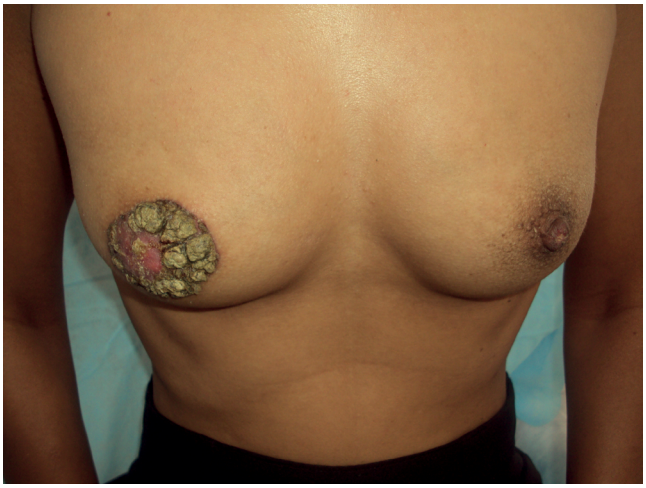

Figure 1. Patient with Paget's disease in the right breast.

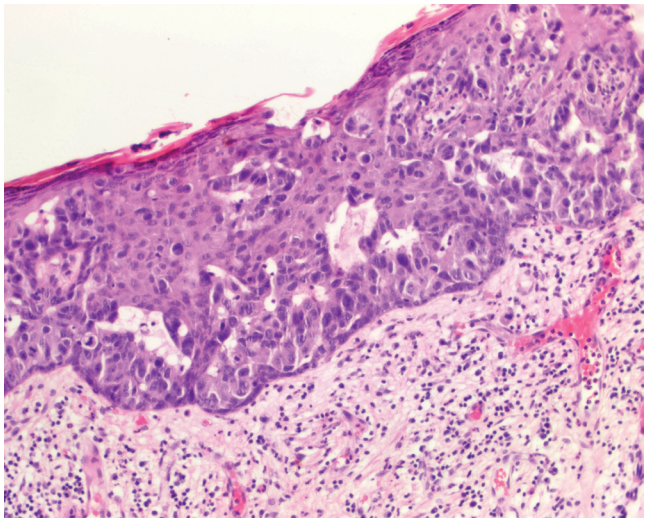

Figure 2. Detail of epidermis with the presence of atypical cells up to the surface (100x).

is a predominance of postmenopausal patients aged between 50 and 60 years. There are reports of PDB in women aged between 24 and 90 years old and, more rarely, in men[3]. The prevalence of PDB is low: it usually corresponds to less than 5% of breast cancers[5]; in our study, the prevalence was 1.9%.

PDB, histopathologically speaking, is characterized by Paget's epidermal cells, which are malignant glandular epithelial cells with abundant and clear cytoplasm, usually containing mucin, pleomorphic, and hyperchromatic nuclei. The number of cells varies from some to large quantities, and it may even completely replace epidermal cells. The invasion of attachment structures may occur. The dermis presents reactive characteristics, such as telangiectasia, chronic inflammation, and ulceration in advanced cases[6]. In our series, the most common differentiation degree was "moderate or high" (83.33%) and the most frequent histological type was "in situ ductal carcinoma" (66.7%).

Regarding immunohistochemistry, the results diverge from the literature as to the hormone receptors, although they all agree that less than 50% of cases have positive activity of these receptors[3,7-9]. In our study, only one patient had positive ERs. The HER-2/neu is associated with worse prognostic in women with breast cancer and, in PDB, it is usually associated with the increased expression of this receptor in nearly all patients (80 to 100%), according to a recent meta-analysis[3,10].

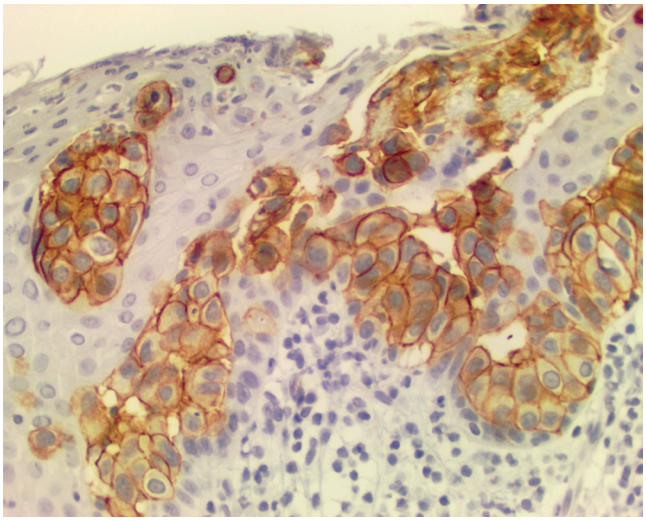

Figure 3. Immunohistochemistry showing positive activity of neoplastic cells to HER-2/neu (200x).

Table 1. Cases series of Paget's disease of the breast.

Case	Age (years)	Skin alteration	Axillary metastasis	CS	Treatment		Lymph nodal condition		Life condition	Follow-up (months)
					Surgery	CT/RT/HT	SL	Lymphadenectomy		
1	78	Yes	No	I	mastectomy	HT	-	16 neg.	Alive and disease-free	74
2	56	Yes	No	II	mastectomy	CT	1 neg.	-	Alive and disease-free	67
3	40	Yes	No	0	mastectomy	-	6 neg.	-	Alive and disease-free	29
4	58	Yes	No	I	Segmental resection	RT	3 neg.	-	L	46
5	57	Yes	No	II	mastectomy	-	1 neg.	-	Alive and disease-free	5
6	67	Yes	No	I	Resection of PAC	-	-	-	Alive and disease-free	104

CS: clinical staging; CT: chemotherapy; RT: radiotherapy; HT: hormone therapy; SL: sentinel lymph node; PAC: papillary-areolar complex; L: lost follow-up contact; neg: negative.

Table 2. Anatomopathological characteristics of cases series of Paget's diseases of the breast.

Case	Type	Degree	ER	PR	HER-2/neu	Ki-67 (%)	Size (cm)
1	ICD	-	Neg.	Neg.	1 +	70	1.5
2	DCis	2	Neg.	Neg.	3 +	90	4.5
3	LCis	3	Neg.	Neg.	1 +	30	0.4
4	DCis	3	Neg.	Neg.	3 +	25	2.0
5	DCis	3	Neg.	Neg.	3 +	-	2.3
6	DCis	3	Pos.	Neg.	1 +	5	0.4

IDC: invasive ductal carcinoma; DCis: ductal carcinoma "in situ"; LCis: lobular carcinoma in situ; Degree: histological degree; ER: estrogen receptor, PR: progesterone receptor; Pos.: positive: Neg.: negative.

In the present study, 50% of the sample had positive activity for the HER-2/neu receptor.

Ki-67 ranged from 5 to 90%, being considerably higher than what was observed in the literature, whose mean is less than 20%; patients with rates higher or equal to 25% have worse overall survival. In the present study, 80% of women with an obtained response had Ki-67 higher than 13.9%[9].

Due to the low incidence of PDB, there are no randomized studies evaluating the best therapeutic strategy. Historically, mastectomy is the recommended surgical treatment, considering the possibility of extensive, multifocal or breast lesions. However, similar results have been observed between mastectomy and conservative surgical techniques in patients' overall survival, although the rate of local recurrence is significantly higher among women undergoing conservative surgery. Prospective and multicentered studies should be carried out in order to assist the surgeon on the most appropriate surgical approach, considering that the description of new oncoplastic techniques and the evolution of mastectomies may change the currently observed recurrence rates[5]. In the present series, the treatment of choice is consistent with the literature[2,4]: all patients underwent surgical treatment; one of them received radiotherapy, one received chemotherapy and another, hormone therapy with tamoxifen.

A recent meta-analysis evaluating the recurrence rate among patients undergoing mastectomy and conservative surgery associated with radiotherapy observed that 13.2% of those who underwent conservative treatments and 5.2% of the ones who underwent mastectomy relapsed[11]. In the present study, no metastatic involvement was observed — neither axillary nor distant —, so the overall survival of patient with mean follow-up of 54 months was 100%. Only one patient had cancer recurrence, 103 months after the initial diagnosis.

CONCLUSION

Due to its rarity and the fact it usually occurs in association with an underlying carcinoma, the PDB should be considered a differential diagnosis of any persistent nipple-areolar alteration. There is no consensus regarding the best treatment of choice. The overall survival rate of patients with a mean follow-up of 54 months was 100%. This is probably due to the absence of axillary and/or distant metastatic involvement.

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CASE REPORT
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BREAST RECONSTRUCTION USING EXPANDER AND FAT GRAFTING AFTER MASTECTOMY ASSOCIATED TO RADIOTHERAPY

Reconstrução mamária com o uso de expansor e lipoenxertia após mastectomia associada a radioterapia

Bruno Bohrer Flores[1]*, Maria del Rosario Sarmiento Piñeres[1], Roberto José da Silva Vieira[2], Carlos Ricardo Chagas[1], Gabriela Volkart Pinho[3]

ABSTRACT

Breast surgery has evolved very rapidly in recent years. New oncoplastic techniques have emerged, which allowed the maintenance of a good approach in surgical treatment of breast cancer, reducing the physical and mental suffering of the patients for presenting better aesthetic results. This case report refers to a 45-year-old female patient who underwent mastectomy and radiotherapy eight years ago due to breast cancer, and had her breast reconstructed with the use of a submuscular expander associated to fat grafting. This study aimed to show a therapeutic option in breast reconstruction.

KEYWORDS: Mammaplasty; mastectomy; radiotherapy; fat grafting.

RESUMO

A cirurgia da mama nos últimos anos evoluiu de forma muito rápida. Novas técnicas de oncoplastia surgiram, o que permitiu manter uma ótima abordagem no tratamento cirúrgico do câncer de mama, diminuindo o sofrimento físico e mental das pacientes por apresentar melhores resultados estéticos. Este relato de caso refere-se a uma paciente do sexo feminino de 45 anos, que foi submetida à mastectomia e radioterapia do plastrão há oito anos, em decorrência de câncer de mama, e teve sua mama reconstruída com o uso de expansor submuscular associado à lipoenxertia.O objetivo deste trabalho foi demonstrar uma opção terapêutica na reconstrução mamária.

DESCRITORES: Mamoplastia; mastectomia; radioterapia; lipoenxertia.

Study carried out at Pontifícia Universidade Católica – Rio de Janeiro (RJ), Brazil.
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INTRODUCTION

Breast surgery has evolved very rapidly in recent years. New oncoplastic techniques have emerged, which allowed the maintenance of a good approach in surgical treatment of breast cancer, reducing the physical and mental suffering of the patients for presenting better aesthetic results.

Breast fat grafting consists of grafting fat, transferring mature adipocytes and stem cells derived from the adipocyte to the region of the breast where it is supposed to cover a defect. It became more frequent in the mid-1990s, with American surgeon Sidney Coleman being the main responsible for systematizing all the preparation required by the technique, from obtaining the materials to grafting the fat in the desired area[1].

Considered a very safe technique, fat grafting aims to improve or correct significant contour deformities after a primary mammary reconstruction[2] or adjuvant treatments, such as radiotherapy[3].

This report presents the case of a 45-year-old female patient who underwent mastectomy and radiotherapy eight years ago due to breast cancer.

CASE REPORT

The 45-year-old patient sought medical consultation wishing to perform reconstruction of the right breast.

She has had a history of breast cancer eight years ago. The treatment consisted of mastectomy of the breast affected by the disease (right breast), complemented by chemotherapy and radiotherapy in the plastron.

The patient wished to perform breast reconstruction in a less aggressive manner, having discarded reconstruction techniques with myocutaneous flap of the large dorsal or the rectus abdominis myocutaneous flap (TRAM flap). These two techniques facilitate the procedure by providing skin from other regions and can replace the portion that has undergone radiation. They also provide muscle, which improves the coverage of the implant, contributing to the softness, the naturalness, the better degree of ptosis and the symmetry with the opposite breast, besides allowing the perception of a soft, warm breast with natural placement and appearance[4].

After discussing the possible surgical techniques with the patient, the option chosen was the placement of a submuscular expander, as well as performing breast fat grafting.

The procedure begins with the collection of fat by liposuction at low pressure with a 60 mL syringe, coupled to the blunt cannula on both flanks (Figure 1). The syringes remain in a vertical position, waiting for the decantation of the material, which is divided into: oily material, live adipocytes, erythrocytes and serum (Figure 2). After complete decanting, only the area in which live adipocytes are found is kept in the syringes, with the rest of the material being discarded.

After carrying out the submuscular lodging for the placement of the implant, and with the Blake drain already fixed, the liposuction material is injected into the subcutaneous tissue.

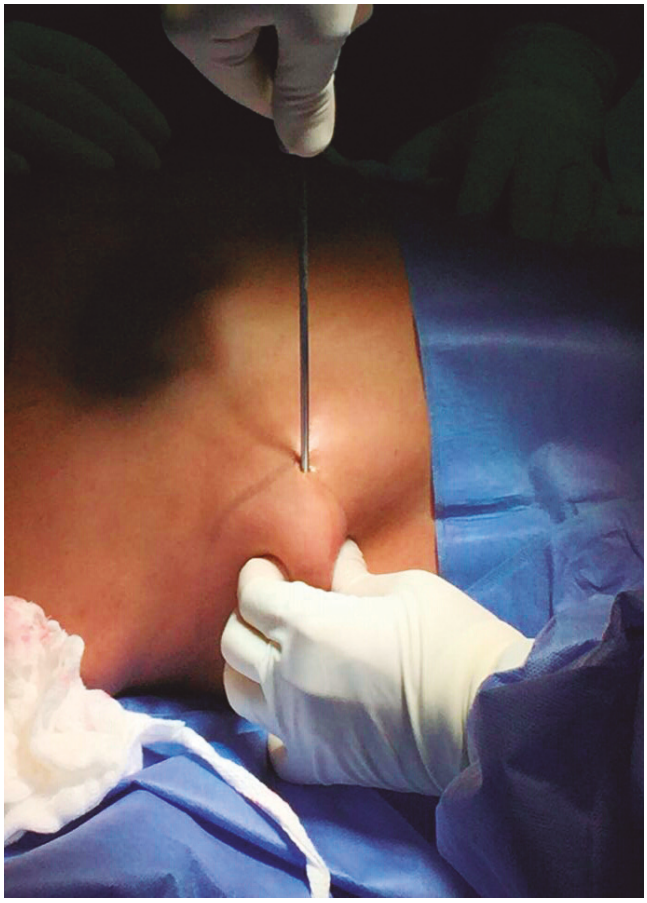

Figure 1. Fat collection by liposuction of flanks.

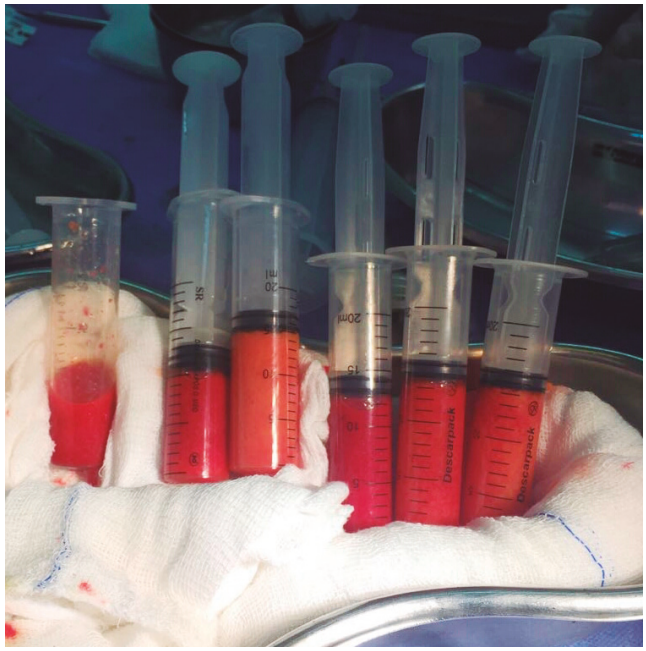

Figure 2. Syringes with collected material, awaiting decantation.

This procedure is done in several directions for an even distribution of fat (Figure 3).

Afterwards, the expander is inserted in the submuscular lodging, and the tissue synthesis is performed by planes: muscular, subcutaneous and skin, presenting the final result shown in Figure 4.

DISCUSSION

Since the 1980s, the late and immediate breast reconstruction technique began to disseminate and, which demonstrated that there is no additional risk to oncological evolution[5].

The musculocutaneous conditions of the chest wall after mastectomy, the degree of involvement of the skin after radiotherapy, the contralateral breast dimension and its ptosis are factors that must be taken into account when evaluating the possibility to use the expander, as poor evaluation may lead to an unsatisfactory aesthetic result[6].

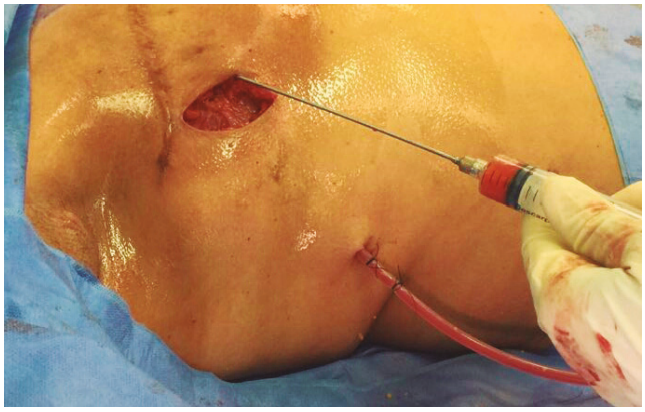

Figure 3. Injection of liposuction material into the subcutaneous tissue.

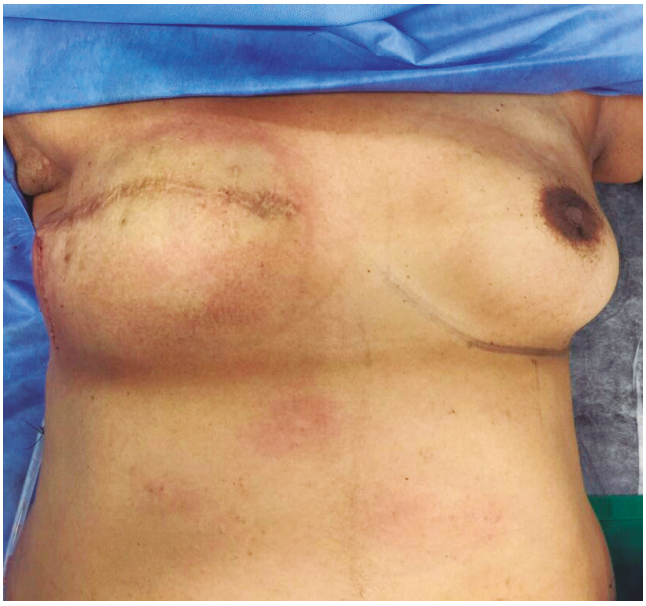

Figure 4. Immediate postoperative result.

The use of tissue expansion causes a gradual stretching of the tissues, allowing subsequent coverage of the new silicone implant with relative abundance of tissue, which would simulate a ptosis in the reconstructed breast, generating a more natural result. Although the expanders are mostly used in late reconstructions, they have been increasingly used in immediate reconstructions. As an advantage, this use removes the surgeon's doubt as to whether the amount of skin remaining from a mastectomy will allow direct placement of a breast implant. In addition, if there is doubt in the performance of postoperative radiotherapy, the expander would serve to maintain the cutaneous framework, preserved in the mastectomy until the conclusion of the treatment[7].

The main indications for breast fat grafting are: correction of post-reconstruction filling defects with implants or flaps; improvement of skin and subcutaneous quality after mastectomy and radiotherapy; correction of filling defects after conservative breast surgery; treatment of post-reconstruction capsular contracture with implants; breast augmentation without the use of allogeneic implants; and improvement of scar quality in the breast[1].

Studies have shown that breast fat grafting does not increase locoregional or systemic recurrence, or a second breast cancer. These findings support the oncological safety of lipofilling and fat grafting in breast reconstruction[8].

When there is the need for image investigation or monitoring, mammography and mammographic ultrasound are performed. It is known that fat grafting causes radiological alterations, but these do not differ from other findings caused by other surgical procedures. Also, there has not been an increase in the number of biopsies performed as a result of such findings[1,9].

Regarding the viability of grafts after fat grafting, most studies estimate that 30 to 40% of the volume is lost after the first procedure, thus requiring subsequent procedures or overcorrection in grafting[9-11].

The rate of complications is low, with fatty necrosis being the most frequent, followed by local infection of the grafted material[9].

CONCLUSION

Breast fat grafting presents a low rate of complications, oncological safety and good aesthetic results, being an important tool in the aesthetic breast treatment.

Its major disadvantage would be the impossibility of accurately measuring the amount of tissue that will be reabsorbed, with many cases requiring several sessions to achieve the desired result.

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CASE REPORT
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IDIOPATHIC GRANULOMATOUS MASTITIS: DIAGNOSIS AND FOLLOW-UP WITH MAGNETIC RESONANCE IMAGING

Mastite granulomatosa idiopática: diagnóstico e seguimento com ressonância magnética

Felipe Eduardo Martins de Andrade[1]*, Rebeca Neves Heinzen[1], Kátia Maciel Pincerato[1], Fábio Arruda de Oliveira[1], Marcos Fernando Docema[1], Carolina Rossi Saccarelli[1], Alfredo Carlos Simões Dornellas de Barros[1]

ABSTRACT

Granulomatous mastitis is a rare and benign condition of the breast that, in some cases, has an unknown etiology of benign inflammatory disease know as idiopathic mastitis. Your diagnosis is usually made by exclusion. Imaging tests have shown nonspecific findings that may suggest an inflammatory disease, a carcinoma, or no changes. A differential diagnosis should be made with other causes of mastitis, always alerting to the risk of inflammatory carcinoma. Imaging tests are more useful to rule out malignancy than to confirm idiopathic granulomatous mastitis. Because both imaging and physical examination can mimic a malignant lesion of the breast, the histopathological report is fundamental to establish the diagnosis. Its etiology remains unknown, so the treatment is controversial in the literature, with some authors recommending surgery, others immunosuppression, and, finally, some antibiotics. We report the case of a 21-year-old woman with a suspected lesion in the breast associated with papillary discharge. During the investigation, there was a 12 x 6 x 8.5 cm enhancement on magnetic resonance imaging associated with inflammatory signs on the skin and lymph nodes. Anatomopathological examination revealed a idiopathic granulomatous mastitis. The enhancement disappeared completely after conservative treatment with corticosteroids. Mammography and ultrasound may also demonstrate nonspecific changes, such as focal asymmetry, undefined mass, or distortion. Despite the limitations of the imaging studies, it has been demonstrated in this report that MRI can be used to monitor the clinical response to conservative treatment and follow-up by the risk of recurrence.

KEYWORDS: Diagnostic imaging; mastitis; granulomatous mastitis.

RESUMO

A mastite granulomatosa é uma condição rara e benigna da mama que, em alguns casos, possui etiologia desconhecida de doença inflamatória benigna, a mastite idiopática. Seu diagnóstico normalmente é feito por exclusão. Os exames de imagens têm demonstrado achados inespecíficos que podem sugerir uma doença inflamatória, um carcinoma ou não apresentar alterações. Deve ser realizado um diagnóstico diferencial com outras causas de mastites, sempre alertando para o risco de carcinoma inflamatório. Os exames de imagem servem mais para descartar uma malignidade do que para confirmar a mastite granulomatosa idiopática. Em função de tanto os exames de imagem como o exame físico poderem simular uma lesão maligna da mama, o laudo histopatológico é fundamental para estabelecer o diagnóstico. A sua etiologia permanece desconhecida, portanto, o tratamento é controverso na literatura, com alguns autores recomendando cirurgia, outros a imunossupressão e, por fim, alguns antibióticos. É apresentado o caso de uma paciente de 21 anos com uma lesão suspeita na mama associada à descarga papilar. Durante a investigação, houve um realce de 12 x 6 x 8,5 cm na ressonância magnética associado a sinais inflamatórios na pele e nos linfonodos. O exame anatomopatológico evidenciou um quadro de mastite granulomatosa idiopática. O realce desapareceu completamente após o tratamento conservador com corticoterapia. A mamografia e o ultrassom também podem demonstrar alterações inespecíficas, tais como assimetria focal, massa indefinida ou distorção. Apesar das limitações dos exames de imagem, demonstrou-se, neste relato, que a ressonância magnética pode ser utilizada para monitorar a resposta clínica ao tratamento conservador e o acompanhamento pelo risco de recorrência.

PALAVRAS-CHAVE: Diagnóstico por imagem; mastite; mastite granulomatosa.

Study carried out at Instituto de Responsabilidade Social do Hospital Sírio Libanês – São Paulo (SP), Brazil.
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INTRODUCTION

There is a great spectrum of breast infection and inflammatory diseases. One of these inflammatory conditions is granulomatous mastitis, which is a rare benign breast condition. There are also some etiologies like tuberculosis, sarcoidosis, parasitic and mycotic infections. In some cases, there is an unknown etiology of an inflammatory disease called idiopathic granulomatosis mastitis (IGM). Kessler and Wolloch first described it as a specific entity in 1972. It occurs in non-lactating young women. The clinical presentation is a local inflammatory sign in the breast. Diagnosis of IGM can be difficult and frequently late. The radiographic evaluation is unspecific, with a variety of presentations. There are some controversies about the best treatment to it. We present the case of IGM with complete response in the magnetic resonance imaging (MRI) follow-up[1-4].

CASE REPORT

A 21-year-old healthy female sought a breast surgeon complaining of a three-month history of cyclic mastalgia and nipple discharge in her left breast. Her menarche was at 13 years-old, with regular menstrual cycles. At the time of admission, she was taking oral contraceptives and denied smoking, alcohol abuse or any preceding breast trauma. Her uncle and maternal grandmother have a history of breast cancer, and her maternal grandfather of hypertension and diabetes. During the physical examination, the patient had breast hyperemia in the inner quadrants of the left breast and a thickened area of approximately 10 cm. The axillary lymph node was extended.

The ultrasound results demonstrated inflammatory signs in the skin, subcutaneous tissue and breast parenchyma on the left side with ductal ectasia (BI- RADS® 2), as seen in Figure 1.

After the dynamic MRI contrast agent, we found an intense enhancement measuring 12 x 6 x 8.5 cm with regional distribution in the inner quadrants, from the nipple to the pectoralis major muscle. The MRI also showed skin edema and lymph node alterations, suggesting an inflammatory process (Figures 2 and 3).

The investigation continued with core biopsy (Figure 1B) and histopathology, which presented a granulomatosis mastitis with giant cells. The cultures were negative for fungi and bacteria (Figures 4, 5 and 6).

The treatment was conservative with corticosteroid therapy for two months. She had complete clinical response afterwards.

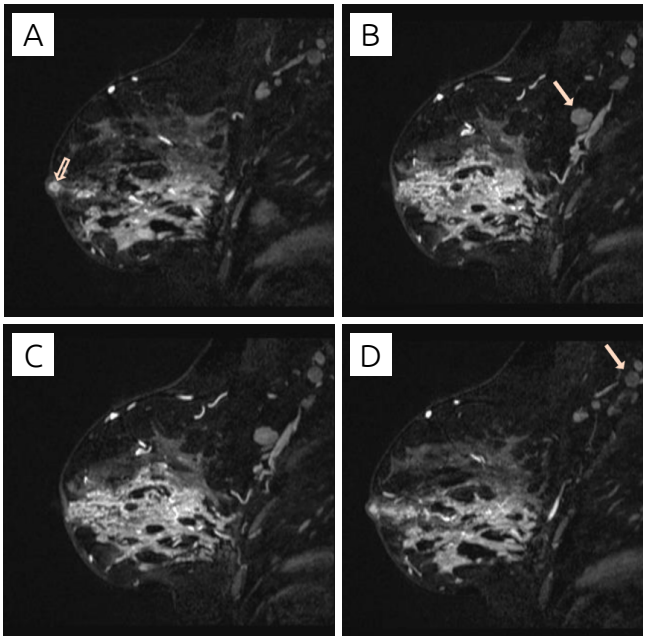

Figure 2. Axial magnetic resonance imaging (A) T1; (B) T2 STIR, skin edema and thickening in lateral quadrants; (C) and (D) subtraction, multiregional enhancement. Ductal ectasia.

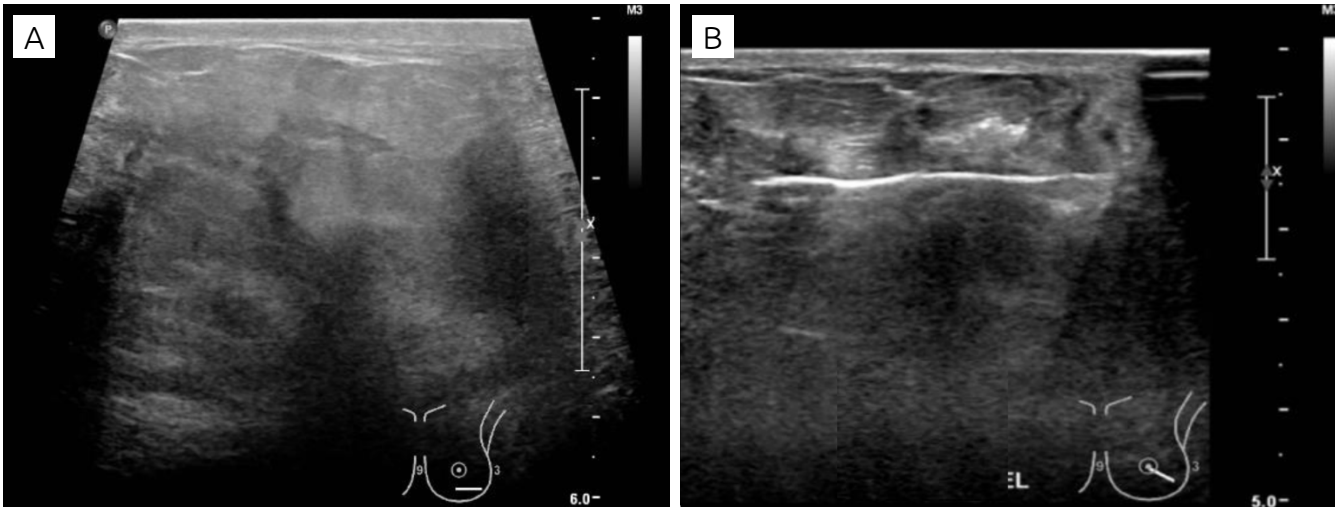

Figure 1. Ultrasound (A) with skin edema and enhancement with parenchymal hyperechogenicity; (B) core biopsy.

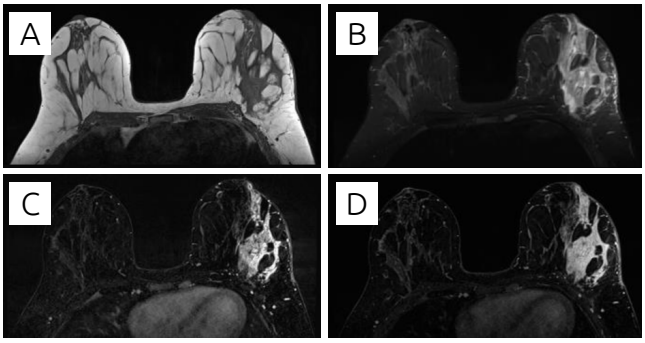

Figure 3. Magnetic resonance imaging enhancement.

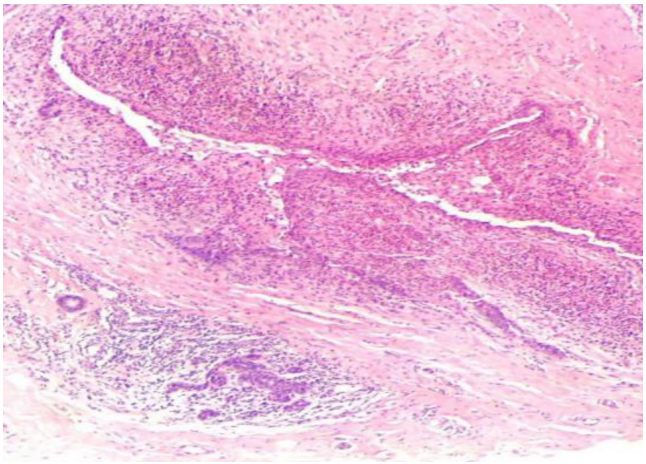

Figure 4. Lobules with inflammation.

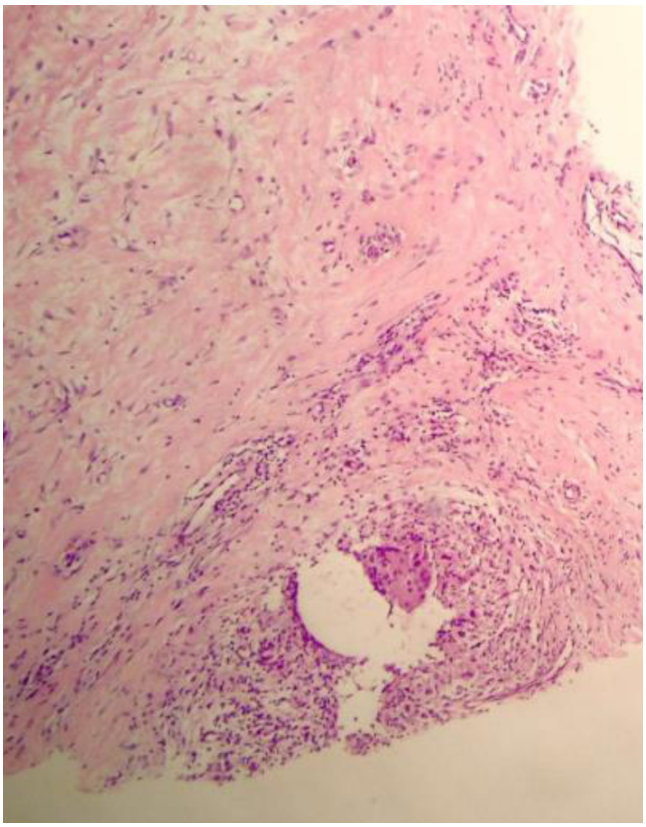

Figure 5. Granuloma with giant cells.

Subsequently, new imaging exams were ordered for follow-up. The new ultrasound showed preserved subcutaneous tissue and skin, and the MRI no longer had enhancements on the left breast (Figures 7 and 8).

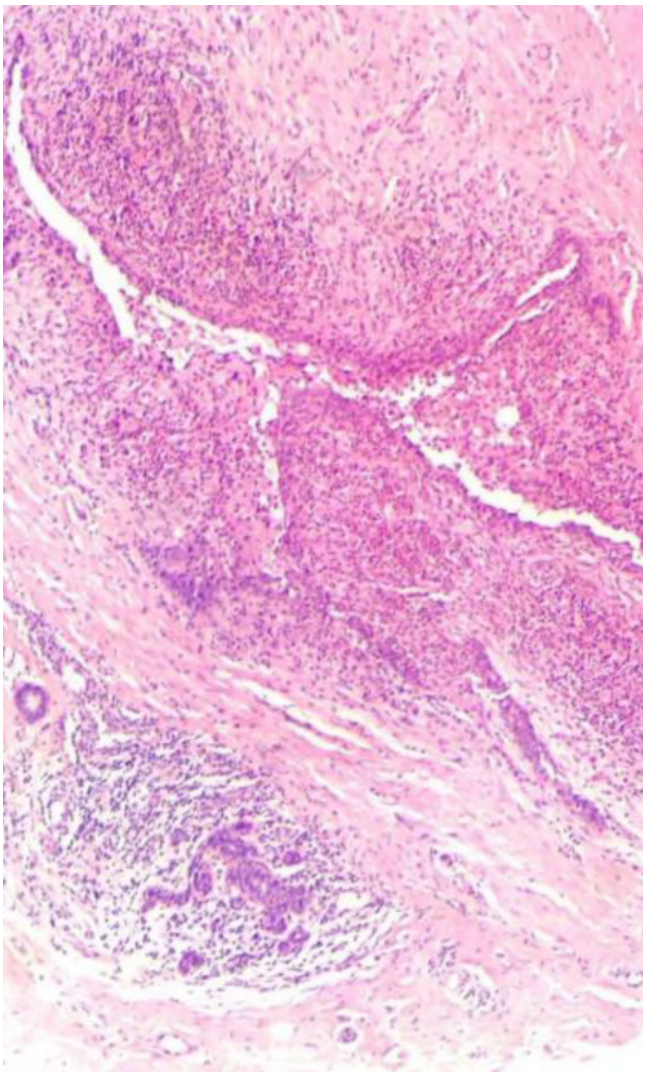

Figure 6. Obstructed duct with inflammation.

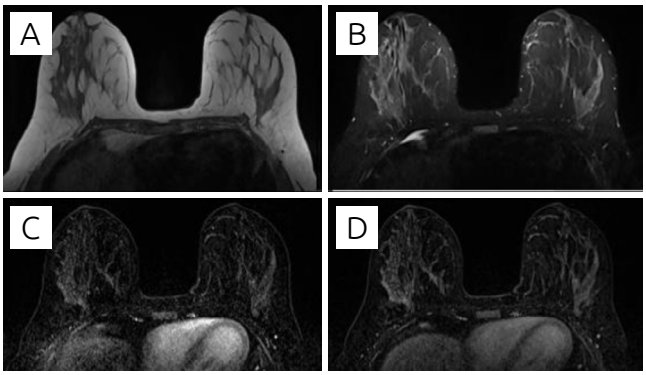

Figure 7. After treatment, axial magnetic resonance imaging (A) T1; (B) T2 STIR; (C) and (D) subtraction, inflammation resolution.

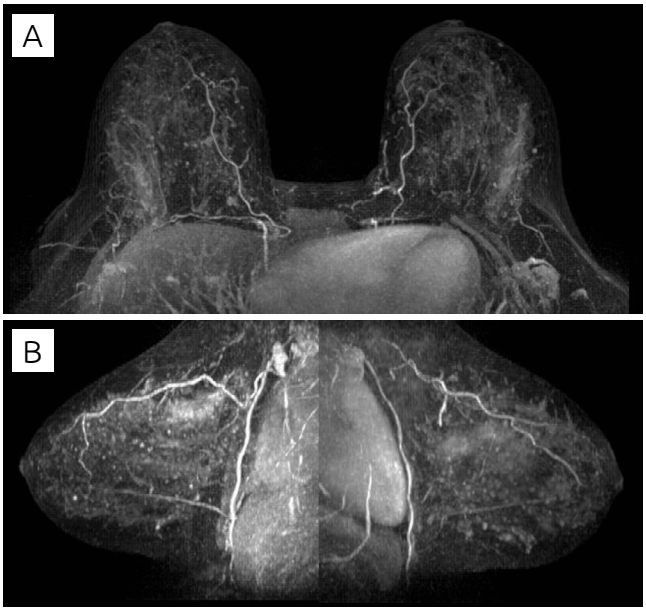

Figure 8. After treatment, MIP reconstruction without suspect enhancements.

DISCUSSION

Large varieties of benign inflammatory and infectious breast diseases are considered mastitis; thus, it is difficult to make a differential diagnosis. Clinicians should be alert to suspected inflammatory carcinoma. Breast mastitis can be lactation and occur during breastfeeding, or nonlactational, which, however, can be an infectious disease, such as tuberculosis, sarcoidosis, cat scratch, Cryptococci and other rare infections or inflammatory diseases like periareolar mastitis, fibrocystic change, or granulomatous mastitis[3,5].

Kessler and Wolloch first reported the IGM in 1972 like a lesion simulating breast carcinoma in five case reports[6]. This is a rare and benign condition, affecting young women, younger than 50 years of age. It is rare and there is a higher racial predilection for Asian and Hispanic women. Some authors believe that it is associated with a recent pregnancy and lactation[1]. Its incidence is unknown. Jayia et al. reported only 17 women at a breast cancer center during a 14-year period, and 2,500 women attended it[2,7-9].

A lump that can mimic carcinoma and can be painful or painless, with single or multiple masses with inflammatory signs like hyperthermia and redness are the main representations. It is usually unilateral and can involve any quadrant, but tends to spare the sub-areolar regions. Kamal et al. showed a predominance of right breast affection as seen in previous reports. In some cases, breast abscess, fibroses and fat necrosis can occur. Reactive axillary lymphadenopathy may also be presented, as in our case report[1,5,8,10,11].

Histology is characterized by a non-caseating granulomatous inflammatory response of the breast lobules in the absence of specific underlying causes. Pathological evaluations demonstrate granulomas, multinucleated giant cells, lymphocytes, plasma cells, micro-abscesses, and fat necrosis[12].

The pathophysiology is not completely understood, but there are some theories. One of them is that a local injury to the ductal epithelium produced by a trauma, infection or irritation can cause an immune response. Other speculated causes are chemical agents, such as smoking, using drugs, trauma and use of contraceptive pills. Oran et al. demonstrated that only one third in their records were smokers and 22% had a history of oral contraceptive use, therefore there is a lack of association[1,3,8].

Diagnosis is done by exclusion of cancer or other infectious diseases. We need to figure out if there is a cause for these alterations. Imaging methods are applied to rule out malignancy rather than to confirm the diagnosis. Unspecific findings may suggest IGM or breast radiologic findings can be normal. The mammogram can show a focal asymmetrical density, ill-defined mass or architectural distortion, and the ultrasound can show a hypoechoic lesion with a posterior shadow and tubular configuration, parenchyma heterogeneity. The MRI can include a parenchymal asymmetry or distortion with different contrast enhancement patterns (diffuse, heterogeneous and ring-shaped enhancement). In our case, the MRI showed a regional enhancement, and because there were other signs in the skin and lymph nodes, an inflammatory process was suggested[1,4,10]. Although radiology findings have a limited value, our report showed that they can be used to monitor the clinical response in a conservative treatment[13].

Because both clinical and radiological presentation can mimic a breast carcinoma, the final diagnosis has to be histopathological; therefore, our patient took a core biopsy. These pathological findings showed that a surgical excision for the diagnosis is not necessary. Other diagnostic forms are performed with fine-needle-aspiration biopsy (FNA) or surgical excisional or incisional biopsy.

The optimal treatment is controversial. In some cases, surgical excision, close observation, immunosuppressant therapy (steroids, azathioprine and methotrexate) and antibiotics are the mainstay of treatment.

Nowadays, surgical treatment has become less eminent and directed to specific cases. Kaviani et al. suggest an algorithm for the management of IGM. They mention that surgical treatments should be restricted to biopsies, by draining the abscess and excising fistulae[14]. They believe that surgical intervention can cause physiological distress, scars, disease exacerbation, fistula formation, and other surgical complications[9,14].

A retrospective study in Phoenix demonstrates that clinical observation can be an effective strategy for this nonmalignant disease, thus avoiding the costs and side effects of surgical and medical treatment[9].

The best dose and duration of medical treatment have not been established. We used the clinical remission to

decide when we should start to decrease the corticosteroid dose until to clinical presentation remission, and finally to its gradual stop. Our patient did not show side effects of the steroid therapy, such as glucose intolerance and Cushingoid features[1,8].

A prospective case series demonstrated a successful treatment in the majority (90%) of women by using only the prednisone therapy[11]. The prognosis is good; nevertheless, local recurrence is frequent[5].

CONCLUSION

We demonstrated the possibility of monitoring granulomatosis mastitis after steroid treatment with MRI.

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CONSENSUS MEETING
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BREAST CANCER SCREENING: UPDATED RECOMMENDATIONS OF THE BRAZILIAN COLLEGE OF RADIOLOGY AND DIAGNOSTIC IMAGING, BRAZILIAN BREAST DISEASE SOCIETY, AND BRAZILIAN FEDERATION OF GYNECOLOGICAL AND OBSTETRICAL ASSOCIATIONS

Recomendações do Colégio Brasileiro de Radiologia e Diagnóstico por Imagem, da Sociedade Brasileira de Mastologia e da Federação Brasileira das Associações de Ginecologia e Obstetrícia para o rastreamento do câncer de mama*

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ABSTRACT

Objective: To present the current breast cancer screening guidelines in Brazil, as devised by the Brazilian College of Radiology and Diagnostic Imaging (CBR), the Brazilian Society for Breast Disease (SBM) and the Brazilian Federation of Gynecological and Obstetrical Associations (FEBRASGO). **Methods:** We analyzed scientific studies available in Medline and Lilacs databases. In the absence of evidence, the guidelines reflected the consensus opinion of an expert panel. **Guidelines:** Annual mammography screening is recommended for women aged 40–74 years. Among women aged 75 years or older, annual mammography screening should be reserved for those with an expected survival of 7 years or more. Complementary ultrasound should be considered for women with dense breasts. Complementary magnetic resonance imaging is recommended for women at high risk. When available, an advanced form of mammography known as tomosynthesis can be considered as a means of screening for breast cancer.

KEYWORDS: Breast Neoplasms; Breast cancer screening; Mammography; Ultrasonography, mammary; Magnetic resonance imaging.

Work performed by the Brazilian National Mammography Commission of the Brazilian College of Radiology and Diagnostic Imaging (CBR) – São Paulo (SP); Brazilian Society of Mastology (SBM), São Paulo (SP); and Brazilian Federation of Gynecological and Obstetrics Associations (FEBRASGO), Rio de Janeiro (RJ), Brazil. This article is the result of a joint guideline between CBR, SBM and FEBRASGO and will be published in the respective journals of these companies.

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RESUMO

Objetivo: Apresentar as recomendações do Colégio Brasileiro de Radiologia e Diagnóstico por Imagem (CBR), da Sociedade Brasileira de Mastologia (SBM) e da Federação Brasileira das Associações de Ginecologia e Obstetrícia (FEBRASGO) para o rastreamento por imagem do câncer de mama no Brasil. **Métodos:** Foram analisados os estudos disponíveis nas bases científicas Medline e Lilacs. Na ausência de dados probatórios, as recomendações refletiram o consenso da comissão de especialistas. **Recomendações:** O rastreamento mamográfico anual é recomendado para as mulheres entre 40 e 74 anos. Acima de 75 anos deve ser reservado para as mulheres que tenham expectativa de vida maior que 7 anos. O rastreamento complementar com ultrassonografia deve ser considerado para as mulheres com mamas densas. O rastreamento complementar com ressonância magnética é recomendado para as mulheres com alto risco. A tomossíntese é uma forma de mamografia que pode ser considerada para o rastreamento do câncer de mama, quando disponível.

DESCRITORES: Câncer de mama; Rastreamento; Mamografia; Ultrassonografia mamária; Imagem por ressonância magnética.

INTRODUCTION

Organized screening programs have led to a reduction in breast cancer mortality in several countries.[1,2] In Brazil, despite all efforts, an increase in both breast cancer incidence and mortality rates has been noticed.[3-5] One peculiarity of breast cancer in Brazil and in other developing countries is that its incidence among women aged 40-50 years is proportionally higher than that reported in developed countries.[6-8]

Programs that aim at standardizing breast cancer screening guidelines – as well as educating the population regarding the importance of such tests – should be promoted. In 2012, the Brazilian College of Radiology and Diagnostic Imaging (CBR), the Brazilian Society for Breast Disease (SBM) and the Brazilian Federation of Gynecological and Obstetrical Associations (FEBRASGO), via the Brazilian National Mammography Commission, published their joint recommendations for breast cancer screening in Brazil.[9]

The purpose of this article is to present an update of those recommendations, based on the most recent and relevant scientific data on the subject.

METHODS

We analyzed studies available in Medline and Lilacs databases to answer the following clinical question: "What impact do mammography, ultrasonography, magnetic resonance and tomosynthesis have on breast cancer screening according to age bracket and personal and family risk?" Our assessment was based on the levels of scientific evidence established by the Oxford Centre for Evidence-based Medicine[10] and on the criteria employed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[11] In the absence of evidence, the recommendations reflected the consensus of an expert committee composed of CBR, SBM and FEBRASGO members.

The recommendations were classified in four categories, according to the degree of scientific evidence and the consensus of th e expert committee, as follows:

- Category A – Recommendation based on strong scientific evidence, with a consistent consensus among CBR, SBM and FEBRASGO members that this recommendation should be strongly supported.
- Category B – Recommendation based on reasonable scientific evidence, with a clear consensus among CBR, SBM and FEBRASGO members that this recommendation should be strongly supported.
- Category C – Recommendation based on little scientific evidence, but with a consensus among CBR, SBM and FEBRASGO members that this recommendation should be strongly supported.
- Category D – Recommendation based on a consensus among CBR, SBM and FEBRASGO members that this recommendation should be supported.

These recommendations will be reviewed every three years.

Recommendations on breast cancer screening in average-risk women

Mammography

- Annual screening with mammography – preferably digital mammography – is recommended for women aged 40-74 years (category A).
- After the age of 75, annual screening with mammography – preferably digital mammography – is recommended for women with an expected survival rate of more than 7 years according to comorbidities (category D).

Ultrasound

- There are no data to support the use of ultrasound scan for breast cancer screening for all average-risk women.

- Ultrasound should be considered as an adjuvant therapy to mammography among women with dense breasts (category B).

Magnetic resonance imaging

- There are no data to support the use of magnetic resonance imaging for breast cancer screening for average-risk women.

Tomosynthesis

- It is recommended that tomosynthesis – when available – be considered in association with digital mammography (combo or synthesized mode) for breast cancer screening (category B).

Breast cancer screening in women at high risk

Mammography

- Women who have a BRCA1 or BRCA2 gene mutation or women who have first-degree relatives with a proven mutation should undergo annual screening mammography for the detection of breast cancer from age 30 onward (category B).
- Women with a projected ≥ 20% lifetime risk – as calculated with one of the mathematical models based on family history – should undergo annual screening mammography starting 10 years before the age at diagnosis of the youngest relative (but not before the age of 30) (category B).
- Women between 10 and 30 years of age with a history of chest irradiation should undergo annual screening mammography from the 8th year after radiotherapy treatment (but not before the age of 30) (category C).
- Women diagnosed with genetic syndromes that increase breast cancer risk (such as Li-Fraumeni syndrome and Cowden syndrome) or women who have first-degree relatives who have been affected should undergo annual screening mammography from diagnosis onward (but not before the age of 30) (category D).
- Women with a history of atypical lobular hyperplasia, lobular carcinoma in situ, atypical ductal hyperplasia, ductal carcinoma in situ or invasive breast carcinoma should undergo annual screening mammography from diagnosis onward (category C).

Magnetic resonance imaging

- Women who have a BRCA1 or BRCA2 gene mutation or women who have first-degree relatives with a proven mutation should undergo annual breast magnetic resonance imaging screening from age 25 onward (category A).
- Women with a projected ≥ 20% lifetime risk – as calculated with one of the mathematical models based on family history – should undergo annual breast magnetic resonance imaging screening starting 10 years before the age at diagnosis of the youngest relative (but not before the age of 25) (category A).
- Women between 10 and 30 years of age with a history of chest irradiation should undergo annual breast magnetic resonance imaging screening from the 8th year after radiotherapy treatment (but not before the age of 25) (category C).
- Women diagnosed with genetic syndromes that increase breast cancer risk (such as Li-Fraumeni syndrome and Cowden syndrome) or women who have first-degree relatives that have been affected should undergo should undergo annual breast magnetic resonance imaging screening from diagnosis onward (but not before the age of 25) (category D).
- Women with a history of atypical lobular hyperplasia, lobular carcinoma in situ, atypical ductal hyperplasia, ductal carcinoma in situ or invasive breast carcinoma could undergo annual breast magnetic resonance imaging screening from diagnosis onward (category C).

Ultrasound

- Ultrasound should be used as a substitute for magnetic resonance imaging in women who, for some reason, cannot undergo the test (category B).

Tomosynthesis

- It is recommended that tomosynthesis – when available – be considered in association with digital mammography (combo or synthesized mode) for breast cancer screening (category B).

Justification

The main benefit of breast cancer screening is the reduction of breast cancer mortality in women over aged more than 40 years. To evaluate the effect of mammography screening on mortality rate, 11 prospective controlled randomized trials have been conducted.[1,2] Except for 2 studies conducted in Canada (Canadian National Breast Screening Study – CNBSS 1 and 2),[12] – which had a strong selection bias for having included a disproportionate number of patients with palpable nodules – all studies showed that the relative risk of death from breast cancer was lower among women who underwent mammography screening than among those who did not.[1,2] The study that showed the largest mortality reduction associated with mammography screening was the Swedish Two-County Trial, which reported a 31% reduction in the mammography screening group after 29 years of follow-up.[13] Several meta-analyses were performed from these studies. In a meta-analysis conducted by the Independent UK Panel, the reduction in breast cancer mortality was estimated at 20%,[14] compared to the 19% reduction reported in another meta-analysis, conducted by a Cochrane center.[15]

On the other hand, the magnitude of the reduction in breast cancer mortality reported in the studies has been questioned by some researchers. Practically, these authors give more consideration to the Canadian studies cited (CNBSS), without considering their flaws. They also argued that most studies were

conducted in the 1960s, 1970s and 1980s, and their results do not express the therapeutic advances that have occurred since then. They speculated that some women who were not screened and died of breast cancer would have survived if they had been treated under the current protocols. They also speculated that therapeutic advances have made the early detection of breast cancer with mammography screening less relevant.[16] However, there is little scientific evidence to support these speculations. It is noteworthy to mention that estimates from studies conducted in the 1970s, 1980s and 1990s also failed to reflect the technological advances in mammography and the potential detection of more curable cancers than in the past.[17,18]

Breast cancer screening for women aged 40-49 years

Major debate occurs in relation to mammographic screening in women aged between 40 and 49. Some studies evaluated the specific impact of mammography screening for breast cancer in this age group. The UK Age Trial, a prospective controlled randomized study, showed a 25% reduction in the relative risk of death in the first 10 years of breast cancer screening in women aged 39-49 years.[19] Hellquist et al. observed – after 16 years of follow-up – a 29% reduction in mortality associated with breast cancer screening for women aged 40-49 years, whereas the reduction reported was of 18% in the subgroup of women aged 40-44 years, and 32% in the subgroup of women aged 45-49 years.[20] In an observational study conducted in Sweden, Jonsson et al. reported that the rate of reduction in mortality associated with breast cancer screening was 38% in women aged 40-49 years.[21] In addition, as previously mentioned, the incidence of breast cancer among women aged 40-50 years in Brazil and other developing countries is proportionally higher than that reported in developed countries.[3,5] Therefore, the CBR, SBM and FEBRASGO recommend that this group of women be included in breast cancer screening protocols in Brazil.

Screening for women aged 74 years and older

The prospective controlled randomized trials failed to include women aged 74 years and older, explaining the lack of direct data on screening for this age group. However, life expectancy for women has increased, with a consequent increase in the incidence of breast cancer among women older than 75 years. Currently, approximately 26% of breast cancer deaths occur in women diagnosed after the age of 74. Another factor that supports the use of mammography screening for this age group is the high sensitivity and specificity of the method.[22,23] Taking into account all these factors, many medical organizations recommend that the decision be made on a case-by-case basis after consulting with the patient. Therefore, the CBR, SBM and FEBRASGO recommend that this group of women with an expected survival rate of more than 7 years be included in breast cancer screening protocols in Brazil.

Breast cancer screening for high-risk patients

When a woman is considered at high risk, breast cancer screening is intensified, which includes two changes compared to screening for the general population. The first change consists of earlier screening, since breast tumors tend to develop sooner among these women. The second change is the incorporation of complementary methods such as magnetic resonance imaging or ultrasound, given the limitations of mammography, which are greater in this group.

Breast cancer screening for patients at high genetic risks

The use of supplemental screening with ultrasound or magnetic resonance imaging has been associated with the detection of a higher number of tumors among women with a BRCA1 or BRCA2 gene mutation, with magnetic resonance imaging proving to be superior to ultrasound.[24-26] A systematic review published in 2007 showed that the sensitivity of mammography and ultrasound was 36% and 40%, respectively, when the methods were used separately, and 55% when they were used in combination. In contrast, magnetic resonance imaging showed a sensitivity of 81% when used alone, and 93% when combined with mammography. Therefore, although nearly 50% of the tumors still went unidentified, the use of ultrasound as an ancillary method was found to increase the number of tumors detected.[27] More recent studies have confirmed these findings. In 2015, Riedl et al. reported that mammography and ultrasound both had an overall sensitivity of 38% when used separately, compared with 50% when they were used together.[28] The authors found that magnetic resonance imaging had 90% sensitivity when used alone, and 93% when combined with mammography. However, they observed no significant increase when magnetic resonance imaging was combined with ultrasound.[28] However, these favorable results can only be achieved if the magnetic resonance imaging scans are of high quality and interpreted by qualified physicians. Another key factor is the continued investigation with a biopsy of the lesions detected only by magnetic resonance imaging or the support of a reference center to perform these procedures.[29,30] Therefore, magnetic resonance imaging is the ancillary screening method of choice for women at high genetic risk and ultrasound should only be used if magnetic resonance imaging cannot be performed for some reason.

Other genetic syndromes

Other genetic syndromes that increase the risk of breast cancer are rare with no specific studies on their relationship with screening for breast cancer. Currently, experts recommend breast cancer screening for women with Cowden, Bannayan-Riley-Ruvalcaba or Li-Fraumeni syndrome, as well as for untested women who have a first-degree relative with any of those syndromes.[24] It is suggested that these women follow a similar screening protocol to that recommended for women with a BRCA1 or BRCA2 gene mutation.

Chest wall irradiation

Women submitted to chest wall irradiation show a higher lifetime risk of developing breast cancer comparable to the risk reported for women with a BRCA gene mutation. However, the risk is variable among these women. The lifetime risk of developing breast cancer shows positive linear correlations with the radiation dose, volume of the field irradiated, and patient age at the beginning of the treatment. In this group, mammography and magnetic resonance imaging complement each other in breast cancer screening.[31] Ng et al. reported that, among these patients, the sensitivity of mammography and magnetic resonance imaging, when used separately, is 68% and 67%, respectively. However, when the two methods are used in combination, the sensitivity increases to 94%.[32] Therefore, it is recommended that all patients exposed to chest wall irradiation before the age of 30 follow a similar screening protocol to that recommended for women with a BRCA1 or BRCA2 gene mutation.

Atypical ductal hyperplasia and lobular neoplasia

Atypical ductal hyperplasia and lobular neoplasms (atypical lobular hyperplasia and lobular carcinoma in situ) are not only precursor lesions, but also risk factors for breast cancer. Their diagnosis may increase the relative risk of developing cancer by 4-10 times.[33,34] There is a consensus that breast cancer screening with mammography should start right after the diagnosis of such lesions. The big issue still under debate is the use of magnetic resonance imaging for breast cancer screening in such patients. The updated recommendations for breast cancer screening of the American Cancer Society (ACS) state that there is no evidence to recommend or contraindicate the use of magnetic resonance imaging. Therefore, the decision regarding its use should be made on a case-by-case basis.[35] However, the number of advocates of the use of magnetic resonance imaging in breast cancer screening is growing. Therefore, it is recommended that women with atypical ductal hyperplasia or lobular neoplasia follow a similar screening protocol to that recommended for women with a BRCA1 or BRCA2 gene mutation.

Personal history of breast cancer

Women with a personal history of breast cancer are at higher risk of developing a second tumor in the treated or in the contralateral breast.[36] In a recent study, the lifetime risk for the development of a second tumor was estimated to be at least 20-25%, a threshold considered by the ACS to classify women as being at high risk and to indicate complementary screening with magnetic resonance imaging.[35] Another study investigated the role of magnetic resonance imaging in women undergoing conservative treatment with negative mammography and ultrasound results. The detection rate was 18 neoplasms per 1,000 women, which is comparable to the detection rate observed in women with BRCA gene mutations. The reported sensitivity and specificity of magnetic resonance imaging for detecting breast neoplasms in women with a personal history of breast cancer are 92% and 82%, respectively.[37] Other authors observed similar values.[38] Therefore, it is recommended that women who received conservative treatment for breast cancer undergo screening with a combination of mammography and magnetic resonance imaging.

Considerations regarding breast tomosynthesis

Tomosynthesis represents a recent step in the evolution of digital mammography, allowing a more accurate evaluation of the breast. Several studies have confirmed the efficacy of tomosynthesis in screening for breast cancer for increasing cancer detection rates as well as reducing false-positive and recall rates.[39-41] The Oslo Trial was a prospective study comparing the combination of tomosynthesis and digital mammography with digital mammography alone. The authors observed that, when the combination of tomosynthesis and digital mammography was used, the cancer detection rate was 27% higher and the false-positive rate was 15% lower, with a consequent reduction in the need for invasive procedures.[40] The STORM Trial compared digital mammography with tomosynthesis associated with digital mammography in a sample of 7,292 women.[41] The authors observed a 51% increase in the breast cancer detection rate and a 17% reduction in the false-positive rate with the use of tomosynthesis. Friedewald et al. retrospectively analyzed 454,850 examinations, of which 281,187 were digital mammograms and 173,663 were tomosynthesis images obtained in 13 centers in the United States.[42] The authors found that the use of tomosynthesis resulted in a 41% increase in the rate of detection of breast neoplasms, mainly primary invasive tumors, with a 15% reduction in the false-positive rate, which has the benefit of reducing screening costs. Other studies corroborated these findings.[43,44]

Some points are yet to be discussed regarding the tomosynthesis protocol. The Food and Drug Administration recommends a combined approach (combo mode) to breast cancer screening, in which conventional digital mammography views (mediolateral-oblique and cranial-caudal) are combined with tomosynthesis acquisition in those same two planes. The dose of radiation, which was the main initial concern, has been shown to be lower than the maximum dose (3.0 mGy per view). Recent studies have demonstrated the efficacy of synthesized mammography, which is a new technique for digital mammography reconstruction based on tomosynthesis images. The use of synthesized mammography maintains the benefits of tomosynthesis while reducing the dose of radiation by nearly half.[45] Therefore, on the basis of data in the literature, the CBR, SBM and FEBRASGO state that tomosynthesis (combo or synthetized mode), when accessible and available, may be considered in breast cancer screening protocols. These data will be reviewed in three years.

CONCLUSION

The reduction in breast cancer mortality, initially recorded in the United States and Europe, is the result of decades of investment focused on early diagnosis and access to appropriate treatment. Breast cancer early detection benefits women with less invasive surgical procedures, increased healing potential and reduced treatment costs. These benefits would keep a significant portion of the female population economically active. It is fundamental that policies aimed at increasing the rate of early detection be implemented in Brazil.

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Steinmacher DI. Evaluation of percutaneous needle biopsy with automatic propellant in the propaedeutics of palpable and nonpalpable lesions of the breast [dissertation]. São Paulo: Federal University of São Paulo. Paulista School of Medicine; 2005.

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