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ABOUT

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CONTENTS

MASTOLOGY IN THE OPEN ENTRANCE OF THE CLOSED PALACE OF THE KING

Mastology na entrada aberta do palácio fechado do rei

Cicero Urban[1]*

Eirenaeus Philalethes is the pseudonym of the English physician, writer and alchemist George Starkey (1628-1665). He studied at Harvard from 1643 to 1649 and practiced medicine in Boston from 1646 to 1650. Starkey, or Philalethes, wrote about 30 important alchemical treatises and influenced names of the wingspan of Isaac Newton and Robert Boyle. The *Open Entrance of the Closed Palace of the King* is one of that, in which Philalethes supposed revealed some of the secrets to the realization of the great alchemical work, *i.e.*, the philosopher's stone[1].

In the first *Mastology*'s editorial, we stated that our journal was born in the shoulders of giants (paraphrasing Newton)[2]. The former *Revista Brasileira de Mastologia* had been a history of success, but it was necessary to change and to try to open an entrance in the closed palace of the international and prestigious journals, the "king" ones in breast diseases. English language was clearly an essential progress, but not enough to transform a Brazilian journal published in Portuguese in an international and respected one. Impact factor (IF) is the scientific community score for the prestige of individual journals. IF journals attract the best manuscripts, and that is our current great challenge.

Then, little more than a year later after *Mastology*'s birth, what happened? We have had a significant increase in the number and in the quality of the articles submitted, and also international editorials from highly respected worldwide authors. As a positive and immediate consequence, our journal became much more attractive to our readers. In the meantime, we also had to face some difficulties inherent to the structural changes of the journal. This whole process was part of the ritual of growing our academic proposal of strengthening.

Now *Mastology* is in the transition to ScholarOne, which is an international comprehensive workflow management system for scholarly journals, books, and conferences. It will increase our profile among authors and peer-reviewers and will decrease our time to publish. This will facilitate the entry of new articles and the rapid peer-review of them. ScholarOne processing is easy to work, fast and allows authors, reviewers and editors to have real-time access to the progress of articles. This is a new and exciting phase for all of us.

The experience of humankind proves that the most beautiful things are the most difficult ones to produce. The "philosopher's stone" in *Mastology* is to have a great and academically respected journal's brand. And the key aspects to that evolution are based on the classical 3 C's of personal brand in leadership, which can be applied to the journal's brand too: consistency, connectedness, and charisma[3]. Consistency is the same of coherence and solidity. Our journal was built in the Brazilian Society of Mastology, which is one of the most important medical societies devoted to breast diseases in the world. The journal is free and has open access, which facilitates its worldwide connectivity and submission of articles. Charisma, the last "C", is an inborn ability of some human beings to be able to charm, persuade, fascinate or seduce another individual through their way of being and acting. Etymologically, the term *charisma* is originated from the Greek *khárisma*, which means "grace" or "favor". A charismatic individual is one endowed with charisma, possessing a set of qualities that characterize him as a remarkable, admirable, or fascinating subject in the eyes of other individuals. Can an academic journal have charisma? I think so, and we are working on it.

Finally, I believe that *Mastology* is already in the open entrance of the closed palace of the king, but now we have many other challenges to face in order to go inside the palace, and, once inside, do everything to stay there.

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TO BOLDLY GO WHERE NO MAN HAS GONE BEFORE
Audaciosamente indo aonde nenhum homem jamais esteve

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In 1,400 a.C., the Babylonians created a time measuring instrument called clepsydra, consisting of two containers with water at different levels (the top one filled with water and the low one empty), with marks indicating the elapsed time. This instrument is considered one of the first "robotic" equipment in history[1].

In medicine, a robot was first used in 1985, when PUMA 560 was used during a brain biopsy to guide the needle. In 1988, the PROBOT, developed at Imperial College London, was used to perform a prostate operation. In 1992, ROBODOC, by the company named Integrated Surgical Systems, accurately carved fittings in a femur during an operation to install a hip prosthesis[2].

A major breakthrough was the need for the US Armed Forces to perform surgeries in the 1990s, with the expectation of having robotic arms in hospitals near the fronts, while in the United States or elsewhere the head surgeon, by using a joystick, would do the procedure. Transmitted over the internet, this data would go to the robot on the battlefield, but the project did not go forward due to limitations in data transmission speed and the impossibility of operating on the battlefield without anyone having to move the robot *in loco*[2].

A major boost in the development of robotic systems was provided by SRI International and Intuitive Surgical with the introduction of the Da Vinci Surgical System and by Computer Motion with the creation of the ZEUS Robotic Surgical System. The first robotic surgery was performed at The Ohio State University Medical Center, in Columbus, under the responsibility of Robert E. Michler. Examples of surgeries performed with the ZEUS system include reconnection of fallopian tubes (1998) and coronary bypass with a beating heart (1999). In 2001 the ZEUS system allowed for the so-called Lindbergh (transatlantic) operation, a cholecystectomy performed by Jacques Marescaux, with the surgeon on the console in New York and the patient in Strasbourg, France[3].

In 2006, the first surgery done exclusively by artificial intelligence was performed, the correction of cardiac arrhythmia, with results superior to that performed by human hands. The machine had a database of about 10,000 similar surgeries and, as its creators said, it was "more than qualified to operate any patient"[4]. In 2010, the Eindhoven University of Technlogy announced the development of the Sofie surgical system, the first surgical robot with force feedback, which allows the surgeon to be sensitive by electronic means[5].

Robotics is such an important science to mankind that, in 2003, Carnegie Mellon University's School of Computer Science, in Pittsburgh, created an award to recognize the great advances in society brought by robotics, whether in real life or in fiction. In 2003, in the first edition of the award, HAL 9000, from the 2001 film A Space Odyssey and R2-D2 from the Star Wars saga were highlighted. In the same year, in real life, Sojourner was honored, a Mars explorer robot launched in 1997, as well as Ultimate, the first industrial robot, that worked on the assembly line of General Motors from 1961. In 2010, the Hall of the Fame honored the Da Vinci robotic system, by Intuitive, the most used robotic platform in surgeries today[6].

In 2015, Antônio Toesca, of the European Institute of Oncology, demonstrated the feasibility and safety of using robotic surgery for performing nipple-sparing mastectomy with immediate reconstruction. He published his results of the first 29 cases performed by a 3 cm incision in the axillary midline, completely hidden by the arm[7]. He was followed by Benjamin Sarfati in France and Hung-Wen Lai in Taiwan. In March 2018, Neil Tanna performed the first procedure in the United States. The Erasto Gaertner Hospital, in Curitiba, has its robotic surgery program since December 2016 in the areas of oncological surgery of the urinary tract, digestive tract and gynecology; and on January 29th, 2019 we performed the first breast procedure, a breast and nipple-sparing mastectomy with immediate reconstruction, thus creating a new option for patients who are candidates for risk-reducing surgeries and early cases of breast cancer.

Traditional surgery requires incisions in the breast, while robotic surgery, in an innovative way, uses this new technology, allowing the procedure to be carried out by a small incision (3 cm) outside the breast, with visual access extended to remote parts of the breast, increasing safety and negligible bleeding.

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With regard to plastic reconstruction, although robotics is still in the embryonic stage, it is quite promising. Traditionally, large dorsal and rectal abdominal flaps require large incisions for dissection. This is a perfect example of the great benefit of robotics, using minimally invasive surgery and significantly reducing scarring of the flap, which even with the use of conventional laparoscopy is not possible because of difficulties in visualization and limitation of movement of the instruments. Micropins, microdoppler probes and hydrojet dissectors are already available, instruments which will increase the use of robots in the field of reconstructive plastic surgery. It should be noted here that the robotic platform also adds magnification with manipulation without tremor[8].

There are almost 5,000 Da Vinci equipment around the world, more than 43,000 trained surgeons and about 5 million surgeries done. In addition, since 1998 we have more than 15,000 publications on robotic procedures. In Brazil, so far, we have 55 Da Vinci systems installed in 46 hospitals and 1 training center.

Cost is still the main constraint for robotic surgery at the moment. The initial investment is about 1.5 million dollars for the equipment, about 2 to 3 thousand dollars in instrument per intervention and about 100 thousand dollars per year for maintenance of the equipment. However, Intuitive's patent is about to fall and new competitors must enter the market, bringing costs to more acceptable levels. The launch of two new equipment, by Medtronic and by Johnson and Johnson, are expected this year.

So, is robotic surgery worth to be used on breast procedures? Like all new technology, we believe that its use should grow over time, always with precise indications. It is another feature that adds to our arsenal in search of the best therapeutic result and the self-esteem of our patients.

Do mastologists need to worry about taking this training? Tough question. Perhaps in large centers that already have robotic programs it is worth developing the experience and using this additional resource. But there is no doubt that the technology has come to stay and that its progress will bring more and more indications and instrumental options.

Let us all be prepared for the future!
And may the science be with you!

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AESTHETIC OUTCOME AND ONCOLOGICAL SAFETY OF NIPPLE-SPARING MASTECTOMY

Resultado estético e segurança oncológica da mastectomia poupadora do mamilo

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Betina Vollbrecht[3] , Francisco Laitano Neto[3] , Felipe Pereira Zerwes[3] , Antônio Luiz Frasson[3]

ABSTRACT

Background: Nipple-sparing mastectomy (NSM) has been performed for breast cancer treatment and for women at high risk. NSM provides better aesthetic outcomes; however, its oncological safety is still controversial. **Objective:** To evaluate the surgical complications, oncological safety and aesthetic satisfaction of breast cancer patients undergoing NSM with immediate breast reconstruction operated by the same medical team in a Breast Cancer Center in Brazil. **Method:** From 2004 to 2011, an aesthetic satisfaction questionnaire was administered to women undergoing NSM followed by immediate breast reconstruction 30 or 60 days after surgery. Aesthetic satisfaction, complication rates and oncological safety were analyzed. **Results:** Thirty-six breast cancer patients who underwent NSMs followed by immediate reconstruction answered the questionnaire. Most of them considered their results good (51%) or great (43%) and all patients will recommend NSM as a therapeutic treatment for other women with breast cancer. Only one patient presented infection and loss of the mammary implant, and recurrence rates were satisfactory (5.5%). **Conclusion:** Our findings showed low complication rate, oncological safety and good aesthetic outcome related to NSM with immediate reconstruction in patients from a Breast Cancer Center in Brazil. Despite the limitations of our study, we support the use of NSM with immediate reconstruction for a better aesthetic outcome with oncological safety.

KEYWORDS: breast neoplasms; esthetics; subcutaneous mastectomy; treatment outcome.

RESUMO

Introdução: A Mastectomia Poupadora do Mamilo (MPM)tem sido realizada em tratamentos de câncer de mama e em mulheres em situação de risco. A cirurgia traz melhores resultados estéticos; todavia, a sua segurança oncológica ainda é controversa. **Objetivo:** Avaliar as complicações cirúrgicas, a segurança oncológica e a satisfação estética de pacientes com câncer de mama submetendo-se à MPM com reconstrução imediata da mama operadas pela mesma equipe médica em um centro de câncer de mama no Brasil. **Método:** De 2004 a 2011, um questionário de satisfação estética foi administrado a mulheres submetidas à MPM seguida de reconstrução imediata de mama 30 ou 60 dias após a cirurgia. Foram analisadas a satisfação estética, as taxas de complicações e a segurança oncológica. **Resultados:** Trinta e seis pacientes com câncer que se submeteram a MPMs seguidas de reconstrução imediata responderam ao questionário. A sua maioria considerou os resultados bons (51%) ou ótimos (43%) e todos os pacientes a recomendarão como tratamento terapêutico a outras mulheres com câncer de mama. Apenas uma paciente apresentou infecção e perda do implante mamário, e as taxas de recorrência foram satisfatórias (5,5%). **Conclusão:** Nossas descobertas mostraram baixa taxa de complicação, segurança oncológica e bom resultado estético relacionado à MPM com reconstrução imediata em pacientes de um centro de câncer de mama no Brasil. Apesar das limitações do nosso estudo, nós apoiamos o uso da MPM com reconstrução imediata para um melhor resultado estético com segurança oncológica.

PALAVRAS-CHAVE: neoplasias da mama; estética; mastectomia subcutânea; resultado do tratamento.

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INTRODUCTION

Breast cancer treatment has made a remarkable progress in the past century. Currently, the surgical treatment of the breast aims at improving the aesthetic outcome and the quality of life while still providing oncological safety. Nipple-sparing mastectomy (NSM) has been successfully performed for the treatment of early breast cancer and for women at high risk[1,2]. The surgical technique of NSM preserves the entire skin envelope and the nipple–areola complex (NAC), allowing the immediate breast reconstruction, which confers better aesthetic results[3]. Despite the concerns regarding the oncological safety of NAC maintenance, current studies have reported similar locoregional recurrence rates and survival outcomes comparing NSM to skin sparing mastectomy and radical mastectomy[4-6].

Several studies have shown better aesthetic outcomes, increased patient satisfaction and improved quality of life associated with NSM[7-9]. However, some authors didn't find better body image outcomes in patients undergoing NSM[10]. In this study, we assess the surgical complications, the oncological safety and aesthetic satisfaction of Brazilian breast cancer patients undergoing NSM with immediate breast reconstruction. Patients' characteristics and aspects of treatment that might be influencing aesthetic outcomes were also evaluated.

PATIENTS AND METHODS

This study was approved by our institutional review board. All patients in late postoperative (more than 30 days) that performed NSM with immediate reconstruction and were operated by the same medical team in a Breast Cancer Center in Brazil (CEMA-PUCRS) were invited to answer the questionnaire; patients who agreed to participate and signed an Informed Consent Form were included in our study. Between 2004 and 2011, 36 breast cancer patients who underwent NSM followed by immediate reconstruction in CEMA-PUCRS were enrolled in the study and given the aesthetic satisfaction questionnaire 30 or 60 days after surgery.

Inclusion criteria for our study included NSM for cancer treatment and risk reduction (Table 1). We collected data on patients' demographics, medical history, family history, tumor characteristics, surgical complications, oncologic and aesthetic outcomes.

Table 1. Nipple-sparing mastectomy (NSM) inclusion/exclusion criteria.

Inclusion criteria	Exclusion criteria
Unilateral or Bilateral NSM Appropriate reconstructive surgery candidate Patient undergoing immediate breast reconstruction Patient in late postoperative (more than 30 days)	Direct nipple involvement with tumor on permanent pathologic exam of a biopsy taken from the remaining major ducts in retroareolar complex Patient not undergoing immediate reconstruction

Surgical procedure

All procedures were performed under general anesthesia using a periareolar or inframammary incision. The skin incision for NSM was chosen in accordance to the main tumor location, method of reconstruction and physician consideration. Approximately 1 cm of tissue was maintained under the nipple to preserve blood flow to the NAC. Histopathological examination of retro-areolar tissue's frozen sections were performed to confirm the absence of malignancy in the retro-areolar margin. A sentinel node assessment was performed when the tumor diameter exceeded 3 cm and in case of high-grade DCIS. Immediate breast reconstruction was performed using silicon prosthetic implants or tissue expanders.

Aesthetic satisfaction questionnaire

Patient's aesthetic satisfaction with NSM outcome was assessed using a simplified questionnaire[11]. There were no validated questionnaires for aesthetic satisfaction at the time of our study. Patients were asked two questions about their satisfaction with the procedure, and if they would recommend this surgical treatment to other breast cancer patients (Figure 1).

RESULTS

Thirty-six breast cancer patients who underwent 60 NSMs followed by immediate reconstruction operated by the same medical time in a Breast Cancer Center in Brazil were included in this study. Twelve (33.3%) patients had a unilateral NSM, while 24 (66.7%) underwent bilateral NSM. Of the 24 patients that performed bilateral NSM to treat breast cancer, 20 (83.3%) went to contralateral prophylactic surgery. Data are summarized in Table 2.

The mean patients' age was 44.2 years (+9.3, range, 23-60). Most patients were Caucasian (n=34, 94.4%) and had a partner (69.4%). The definitive histology was invasive ductal carcinoma (IDC) in 16 cases (44.5%), ductal carcinoma *in situ* (DCIS) in 7 cases (19.4%), lobular carcinoma *in situ* (LCIS) in 3 cases (8.3%), invasive lobular carcinoma (ILC) in 4 cases (11.1%) and other in the remaining cases (16.7%). Surgical margins were clear in all cases.

A small fraction of patients (11.1 %) had undergone radiotherapy before surgery to treat previous breast carcinoma, and in 11 patients (30.6%) adjuvant radiotherapy was administered. Most of these patients presented invasive ductal carcinoma (IDC) with high histologic grade and underwent radiotherapy to reduce the risk of local recurrence. All patients did transoperatory anatomopathological exam of the retro-areolar border for NAC tumor investigation and none of the cases was compromised needing NAC removal. From all 36 patients, 19 were treated with chemotherapy, 3 (8.3%) with neoadjuvant chemotherapy and 16 (44.4%) with adjuvant chemotherapy. Seventeen patients (47.4%) did not receive systemic therapy. There was no delay in starting the adjuvant treatment.

All patients underwent immediate breast reconstruction. Silicone implant was used in 25 patients and a tissue expander was used in 11 patients. Patients submitted to unilateral NSM had a symmetrization on the contralateral breast. The average time between expander placement and change to definitive prosthesis was 10.2 months.

When patients were asked about aesthetic satisfaction after NSM, 51% considered a good aesthetic outcome, 43% found it great, 6% reasonable and none considered bad or terrible. All patients answered they would recommend NSM as a therapeutic treatment for women with breast cancer. Among the patients who underwent bilateral NSM (n=24), 58.3% were satisfied with the aesthetic outcome in the operated breasts. Only one patient was more satisfied with the aesthetic outcome of NSM in the breast with cancer than in the healthy breast (contralateral prophylactic surgery). All other patients were more satisfied with the aesthetic outcome of the breast that went through prophylactic surgery. This difference was statistically significant (p<0,001). No significant difference in aesthetic satisfaction was found when comparing patients with a partner versus those with no partner (p=0.625), patients submitted to chemotherapy versus no chemotherapy (p=0.503), young patients versus old patients (p=0.99), and time to fill the questionnaire (30 days versus 60 days) (p=0.955).

Prophylactic antibiotics (cephalosporin) were administered for 7 days postoperative and the average time of hospitalization was 3 days. There was no case of NAC necrosis or of hematomas with drainage necessity. Only one patient (2.7%) presented infection and loss of the mammary implant.

After a mean follow-up period of 23.6 months (range, 5–46 months), two patients presented local recurrence, both in the NAC (5.5%). One of them presented Paget's disease nine months after surgery and the other presented DCIS after 12 months of follow-up. Both patients underwent NSM for DCIS treatment with no adjuvant radiotherapy. Only one patient developed distant metastasis (liver metastasis) (2.7%) with 19 months of follow-up. At the end of the follow-up period, the overall survival was 100%.

DISCUSSION

Our study assessed the complication rate, oncological safety and aesthetic satisfaction of 36 Brazilian breast cancer patients undergoing 60 NSM with immediate breast reconstruction operated by the same medical time in a Breast Cancer Center in Brazil.

Corroborating previous literature, our results showed high aesthetic satisfaction following NSM with immediate reconstruction. Systematic review evidenced that after bilateral prophylactic mastectomy, patients were satisfied with the aesthetic outcome and reported a positive body image[7]. Howard and colleagues showed high levels of aesthetic satisfaction in patients undergoing NSM for cancer treatment and risk-reducing surgery using the BREAST-Q questionnaire. Thirty-nine patients filled this questionnaire prior to surgery and 2 years after the completion of reconstruction. Patients who underwent risk-reducing NSM presented a higher overall satisfaction. However, the overall satisfaction with breasts was similar in both groups in postoperative. These results were not impacted by the occurrence

Patient satisfaction assessment questionnaire
Nipple sparing mastectomy and immediate breast reconstruction: Breast cancer patients and high risk patients
1. How do you classify your satisfaction with aesthetic outcome of the surgery you went through in a scale of 5 levels?
Really bad ( )
Bad ( )
Reasonable ( )
Good ( )
Great ( )
2. Is there a difference in your satisfaction, related to the aesthetic outcome, between the right and the left breasts? If yes, which breast do you think has the best aesthetic outcome? (Only for patients that did bilateral procedure)
Yes ( )
Right ( )
Left ( )
No ( )
3. Would you recommend this treatment to another patient?
Yes ( )
No ( )

Figure 1. Patient satisfaction assessment questionnaire.

of complications8. In accordance, Bailey and colleagues demonstrated higher scores in patient aesthetic satisfaction and better outcomes in 32 breast cancer patients who underwent

Table 2. Patient's demographics.

Characteristics	NSM (%)
Number of patients	36
Mean age ± SD, year	44.3 ± 9.3
Race	
White	34 (94.4)
Black	1 (2.8)
Asian	1 (2.8)
Partner	
Yes	25 (69.4)
No	11 (30.6)
NSM	
Unilateral NSM	12 (33.3)
Bilateral NSM	24 (66.7)
Cancer stage	
0	10 (27.9)
I	12 (33.3)
II	12 (33.3)
III	2 (5.5)
Cancer histology	
DCIS	7 (19.4)
LCIS	3 (8.3)
IDC	16 (44.5)
IDC+DCIS	1 (2.8)
ILC	4 (11.1)
Phyllodes	1 (2.8)
Mucinous carcinoma	2 (5.5)
Tubular carcinoma	1 (2.8)
Medular carcinoma	1 (2.8)
Radiotherapy	
Previous RT	4 (11.1)
Adjuvant	11 (30.6)
None	21 (58.3)
Chemotherapy	
Neoadjuvant	3 (8.3)
Adjuvant	16 (44.5)
None	17 (47.2)
Immediate reconstruction	
Immediate implant	25 (69.4)
Immediate tissue expansor	11 (30.6)

SD: standard deviation; NSM: nipple-sparing mastectomy; DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; RT: Radiotherapy.

NSM compared to 32 breast cancer patients who underwent non-NSM using the BREAST-Q questionnaire[9]. More than 94% of our patients who underwent NSM with immediate reconstruction considered the aesthetic outcome good or great, and all of them would recommend the same surgical treatment for other patients with breast cancer. These findings support the aesthetic consideration of NSM's use.

Most of the NSMs performed were bilateral (66.7%); most of the patients with unilateral breast cancer underwent contralateral prophylactic NSM (70.8%). The use of bilateral NSM seems to provide a better aesthetic outcome and to reduce the risk of cancer recurrence on contralateral breast. However, the survival benefit remains unclear in the literature[12-14]. In agreement with our findings, several authors reported high satisfaction in patients undergoing CPM[15-17]. Most of the patients who underwent bilateral NSM (97.2%) were more satisfied with the aesthetic outcome of the breast that went through prophylactic treatment. Radiotherapy might be affecting negatively the aesthetic outcomes of the irradiated breast[18,19]. The immediate reconstruction offers a better aesthetic outcome when radiotherapy is not performed. Radiotherapy prior or post-mastectomy induces capsule formation in 85% of patients, affecting the aesthetic outcomes[20].

We also analyzed factors that could be influencing on patients' aesthetic satisfaction after NSM. The presence of a partner, chemotherapy treatment, age, and different time to answer the questionnaire were not associated with the patients' aesthetic satisfaction.

Furthermore, this study presents infection with loss of mammary implant in one patient and no cases of NAC necrosis. The complication rate presented in our study was of 2.7%, which is lower compared to previous works[1,21,22]. In NSM performed for treatment of breast cancer and risk reduction, the overall complication rate was approximately 5.3% with infection rate of 4.3%[21].

During follow-up, NAC recurrence rate was 5.5% and systemic recurrence rate was 2.7% with no effects on overall survival. Both patients that relapsed underwent NSM for DCIS treatment with no adjuvant radiotherapy. A systematic review found a pooled local recurrence of 2.38% after a mean follow-up of 38 months (range, 7.4–156 months)[22]. Another study presented no cases of local recurrence and NAC recurrence in a median follow-up of 49 months[21]. An analysis of NSM from the Italian National database reported a local regional recurrence rate of 2.9% with a recurrence rate in NAC of 0.7%[23]. The recurrence rates reported in our study were acceptably higher considering that we analyzed all the indications to the procedure and took into account that our analyses were based on patient numbers, and not on procedure numbers as most of the studies. The authors had no conflict of interest with this study.

There were several limitations to this study. We did not use a comparison group of mastectomy patients not having a nipple-sparing mastectomy. Our study presented a small sample size

and only patients who returned to the Breast Cancer Center of the study after 30 or 60 days post-operation and accepted to participate were selected. The questionnaire used was based in previous works; however, this instrument was not validated. In the beginning of our study, no validated aesthetic questionnaires were available. We chose to use a summary questionnaire to increase patients' adherence to our research, but the sensitiveness of the instrument could be diminished.

CONCLUSION

Our findings showed oncological safety and good aesthetic outcomes related to NSM with immediate reconstruction in patients from a Breast Cancer Center in Brazil. Complication rates were low when compared to previous literature and recurrence rates were satisfactory. Despite our study's limitations, we support the use of NSM with immediate reconstruction for better aesthetic outcomes with oncological safety.

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EVALUATION OF LOCAL RECURRENCE OF BREAST CONSERVATION SURGERY AT THE CEARÁ INSTITUTE OF CANCER

Avaliação da recidiva local da cirurgia conservadora de mama no Instituto do Câncer do Ceará

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ABSTRACT

Introduction: Breast cancer is the most common malignant tumor in the world, with the exception of cases of non-melanoma skin cancer. In Brazil, more than 56,000 cases were estimated for 2016. The expected mortality rate remains high because of late diagnosis. Nowadays, conservative surgery is the gold standard treatment. **Objective:** To evaluate the locoregional recurrence of conservative surgery practiced at the Ceará Institute of Cancer, between 2002 and 2012. **Method:** A cross – sectional study with a descriptive approach using secondary data obtained from the medical records of patients with breast cancer operated at the Ceará Institute of Cancer. **Results:** The study population consisted of 360 patients. Invasive ductal carcinoma was the most common type (72.8%), followed by ductal carcinoma in situ (16.4%) and invasive lobular carcinoma (4.7%). The other histological types represent 6.4% (cribriform, 0.5%, medullary, 0.6%, micro invasive, 0.3%, mucinous, 1.1%, papillary, 3.1% 8%; and tubular, 0.8%). In the sample, 25 patients had some type of recurrence: 13/360 (3.6%), local or locoregional; and 12/360 (3.3%), distant recurrence. **Conclusion:** From the data analysis, we can conclude that the conservative surgery practiced at the Ceará Institute of Cancer showed data on recurrence compatible with the international literature.

KEYWORDS: Carcinoma, ductal, breast; mastectomy, segmental; recurrence

RESUMO

Introdução: O câncer de mama é o tumor maligno que mais acomete mulheres em todo o mundo, excetuando-se os casos de pele não melanoma. No Brasil, estimavam-se mais de 56.000 casos para 2016. A mortalidade esperada ainda é alta devido ao diagnóstico tardio. Na atualidade, a cirurgia conservadora é o padrão-ouro. **Objetivo:** Avaliar a recidiva locorregional da cirurgia conservadora praticada no Instituto do Câncer do Ceará, no período entre 2002 a 2012. **Método:** Estudo transversal e descritivo, utilizando dados secundários obtidos nos prontuários médicos de pacientes com câncer de mama operadas no Instituto do Câncer do Ceará. **Resultados:** A população em estudo foi de 360 pacientes. O carcinoma ductal invasivo foi o tipo mais comum (72,8%), seguido do carcinoma ductal *in situ* (16,4%) e do carcinoma lobular invasivo (4,7%). Os outros tipos histológicos representam 6,4% (cribiforme, 0,5%; medular, 0,6%; microinvasor, 0,3%; mucinosos, 1,1%; papilífero, 3,1%; e tubular, 0,8%). Na amostra, 25 pacientes tiveram algum tipo de recidiva: 13/360 (3,6%), local ou locorregional; e 12/360 (3,3%), recidiva a distância. **Conclusão:** Da análise dos dados, podemos concluir que a cirurgia conservadora praticada no Instituto do Câncer do Ceará tem dados de recorrência compatíveis com a literatura internacional.

PALAVRAS-CHAVE: Carcinoma ductal de mama; mastectomia segmentar; recidiva.

INTRODUCTION

Breast cancer is the most common malignant tumor in the world, with the exception of cases of non-melanoma skin cancer. It is the fifth leading cause of death due to cancer in the world (522,000 deaths). In Brazil, mortality rates from this type of cancer continue to increase. One of the probable factors for the continues growth of these rates is due to late diagnosis. 57,960 new cases are estimated for the year 2016, according to data from the National Cancer Institute (INCA).[1] Radical surgical treatment for breast cancer was the universally accepted surgery for several decades. Idealized by Willian Halsted,[2] this surgery removed the entire mammary gland along with the skin and its adjacent tissues, major and minor pectoral muscles, as well as all lymphatic drainage from the axillary region and the neck (supraclavicular fossa).

In 1973, the NSABP B06 study was commenced to evaluate the efficacy of conservative surgery in women with early breast cancer (EC I and II) and tumors <4 cm. Women were randomized for conservative surgery, with or without radiotherapy and total mastectomy.[3,4]

Between 1973 and 1980 Veronesi et al., independently randomized 701 women with tumors <2 cm and clinically negative axilla for a Halstead mastectomy or for conservative surgery with axillary lymph node dissection and radiotherapy.[5] From the data accumulated in these studies and the research of Veronesi et al. - Milan I and Milan II -,[5] conservative surgery presented with an oncologically safe alternative to radical surgery.

Thus, conservative surgery associated with systemic treatment and radiotherapy has overall survival rates similar to the radical surgery proposed by Halsted over 100 years ago.

The objective of this study is to evaluate the local recurrences and risk factors for recurrences after conservative surgeries performed at the Cancer Institute of Ceará, from 2002 to 2012.

METHOD

A cross-sectional study with a descriptive approach based on secondary data obtained from medical records of breast cancer patients submitted to conservative surgical treatment with sentinel lymph node biopsy or axillary lymph node dissection at the Ceará Institute of Cancer between 2002 and 2012. Regarding eligibility, a sample of patients with previous breast cancer diagnosis, including those with ductal carcinoma in situ (DCIS), obtained by surgical biopsy or core biopsy, was performed from the study population.

Patients submitted to radical or modified radical surgeries, those whose files had insufficient data, were submitted to neoadjuvant therapies and surgeries performed in case of recurrence or that missed the follow-up, were excluded from the analysis.

The independent variables studied were age, histological type, histological grade, angiolymphatic invasion, tumor dimensions, axillary status, surgical margin, adjuvant treatments performed and local control.

In the sentinel lymph node evaluation, a 0.8 mL of 99mTc-, 29.6 mBq (0.8 mCi) was injected intradermally in the periareolar area, in the four cardinal points of the affected breast. After lymphatic migration, the sentinel lymph node was located with the help of a gamma probe, removed and sent to the pathologist, and then sliced longitudinally, up to 2 mm along its long axis, subjecting all fractions to histological examination, without immunohistochemical study.

In the evaluation of the breast quadrant, the piece was resected with a macroscopic safety margin of approximately 1 cm in the palpable lesions and, in the impalpable, with the aid of blue staining or radioguided occult lesion localization (ROLL), in order to maintain the lesion within the resected mammary sector and maintain oncological safety.

All margins of the section were evaluated (cranial, caudal, medial, lateral, deep and superficial). The pathologist measured the tumor and its distance from the margins macroscopically. The edges were frozen and microscopic evaluation was performed. In the case of compromised margins, margin widening was performed, usually at the same surgical time.

The data were stored in the database of the Statistical Package for Social Science (SPSS®) for Windows, version 21.0. For the characterization of the results, absolute (N) and relative (%), medium and median frequencies were used. The χ^2 test was used in the analysis of association between the categorical variables. For frequencies smaller than five or of small size, this test was replaced by Fisher's exact, when appropriate. The exact values of p were obtained from the distribution of χ^2, when applicable, excluding cases categorized as "ignored", "unknown" or "unassessable" of each variable studied. A significance level of 5% was adopted. This research was registered under process number 011/2012 and was approved by the Research Ethics Committee of the Ceará Institute of Cancer, according to opinion number 61,473, of July 26, 2012.

RESULTS

The study population consisted of 360 patients with primary breast cancer submitted to conservative surgery. Invasive ductal carcinoma was the most common histological type, with 262 patients (72.8%), followed by DCIS, with 59 (16.4%) and invasive lobular carcinoma, with 17 (4.7%). The other histological types together represent 6.1% (cribriform, 0.5%, medullary, 0.6%, micro invasive, 0.3%, mucinous, 1.1%, papillary, 3.1%, and tubular, 0.8%).

Within the analyzed sample, 25 patients (6.9%) had some type of recurrence (local, locoregional or distance): 12 (3.3%), distance; 11(3.1%), local; and 2 (0.6%), locoregional. From this recurrence group, 20 (80%) occurred within the first 5 years of follow-up; 3 (0.12%), between 5 and 10 years of follow-up; and

1 (0.04%), with less than 2 years of follow-up. Among the patients with recurrence, 21 (84%) had invasive cancer (20 with invasive ductal carcinoma - 95.2% of the cases - and 1 (4.8%) with invasive lobular carcinoma) and 4(16%) had DCIS. Among those patients with invasive cancer 11 were alive in the last evaluation (October 2013), 2 left the follow-up and 8 died, with the primary cause of death being breast cancer. Among the patients whose primary cancer was DCIS, 3 were alive (75%) and 1 (25%) had died. In the group of patients with recurrences, 2 (8%) presented compromised margins of the primary cancer in surgery, while 23 (92%) had free margins.

Among the 360 patients in this sample who underwent conservative surgery, 186 (51.7%) were submitted to a chemotherapy regimen: 29 (8.1%), adriamycin / cyclophosphamide (AC); 27 (7.5%), AC with taxanes; 66 (18.3%), cyclophosphamide, methotrexate and fluoroacil (CMF); 40 (11.1%), fluoroacil, adriamycin and cyclophosphamide / fluoracil, epirubicin, cyclophosphamide (FAC / FEC); and 9(2.5%), to other regimes. Within the recurrence group, 21 patients (84%) underwent chemotherapy and 18 (72%) had an association with hormone therapy.

Regarding radiotherapy treatment, 42 patients (11.7%) were not submitted to radiotherapy; the remainder - 318 (88.3%) - was. In the recurrence group, 22(88%) received radiotherapy while three patients (12%) were not submitted to radiotherapy

SPSS® (version 20.0) was used for the statistical analysis of data. The χ^2 test was used to compare the frequencies, or the Fisher's exact test. The level of significance was 95% - the bilateral p value <0.05 (p <0.05) was considered statistically significant.

The analyzed variables were: age, number of positive sentinel lymph nodes, radiotherapy, histological type and degree of primary cancer differentiation, primary and recurrence surgical approach, performed chemotherapy, presence of hormone receptors (estrogen and progesterone), sentinel lymph node with capsular extravasation, axillary lymphadenectomy, clinical and pathological staging of the primary cancer, angiolymphatic invasion, surgical margin and presence of the HER-2 protein.

The only variables in this sample that had a positive association with recurrence were sentinel lymph node with capsular extravasation (p = 0.044) and angiolymphatic invasion (p = 0.057) in the Fisher's test. However, due to its characteristics, we can use the likelihood ratio that would give a significant ratio (X = 4,104, p = 0.043).

In this evaluation, it was expected that there would be a positive relation between the staging of the primary cancer (both pathological and clinical), histological grade, number of positive sentinel lymph nodes, as well as age.

This statistical significance may not have occurred due to the n that, although significant (n = 360), is presented as a small sample, since, with current treatments, recurrence of breast cancer ranges from 0.5 to 1% year. Thus, we would need a much larger patient sample for there to be statistical significance.

DISCUSSION

In the last few decades, the progress in breast cancer treatment has undergone important changes, prolonging the life of patients, as well as the improvement in the quality of life of those patients with this disease.

The role of conservative surgery is well established in the scientific community regarding the association between oncological safety and the esthetic effect.

Veronesi et al.[5] showed in their study that patients with T1 / T2 N0M0 primary cancer could undergo conservative surgery and that this treatment modality would not affect overall or disease-free survival. In a study by Milan I, better local control of the disease was found in patients treated with conservative breast surgery and local treatment with radiotherapy. The main disadvantage of conservative breast surgery was local recurrence, which varied from 6 to 16%. Several studies have shown that the rate of local recurrence after conservative surgery is declining. The explanation for this observation is multifactorial, including careful evaluation of the margins, use of more personalized and accurate radiotherapy in the tumor bed, and more patients receiving systemic therapy.[6-8]

The use of new combinations of systemic adjuvant therapies and the use of trastuzumab may have resulted in an additional improvement in local control, especially in young patients.[9] In a population-based study, Voogd et al.[10] evaluated the risk trends for local recurrence and the impact of local or distance recurrence on disease-free survival in patients with primary breast cancer aged <40 years. The rate of local recurrence declined from 9.8% in the period 1988-1998 to 5.9% between 1998-2005 and 3.3% in 2006-2010.[8]

Successful conservative surgery requires the complete removal of the malignant tumor, including a margin of normal breast tissue. This can be challenging since the microscopic spread of cancer can be difficult for the surgeon to discern. The National Comprehensive Cancer Network (NCCN, version 3.2015)[11] says that adequate surgical margins are those above 10 mm. There is no consensus for the interval between 1 and 10 mm. Margins less than 1 mm are considered inadequate. In the last consensus by St Gallen, [12] a margin is considered adequate when it does not touch the ink during the freezing process.

In a retrospective study published in the journal of the international society of surgery,[13] the margin was not a significant factor regarding the impact of patient survival. The biological characteristics were more important (histological type, hormonal receptors, presence of HER-2 protein and lymph node status).

In the study under analysis, 25 patients (7.5%) had some type of recurrence, 13 of which had local or locoregional recurrence (13/360 - 3.6%) and 12, distance recurrence (12/360 – 3.3%), which is in accordance with data from the international literature.

In the analysis of the recurrence group, only 3 patients (1.2%) were not treated with radiotherapy. It can be observed that among

the 360 patients submitted to conservative surgery, 42 (11.67%) did not perform this type of treatment.

Regarding chemotherapy, 174 patients (48.3%) did not receive chemotherapy treatment. In the recurrence group, 5(20%) did not undergo treatment with any chemotherapeutic agent.

The current research is limited, to a certain extent, because of the lack of data in relation to Ki 67, since some patients were not submitted to this analysis because the immunohisto-chemical studies with all the predictive and prognostic factors only became standard procedure in the institution from 2006. Therefore, an analysis of the molecular classification of these patients is impossible.

CONCLUSION

Surgery for breast cancer remains in evolution. Over the years, studies have taken us from radical procedures to those with the least mutilation possible and immediate local repair.

It can be concluded from this research that the conservative surgery practiced at the Ceará Institute for Cancer between 2002 and 2012, achieved data on local, locoregional and distance recurrence compatible with the international literature.

We also emphasize the importance of the continuity to this study to contribute to the improvement of the quality of life of the patients, in relation to their image and self-esteem after breast cancer treatment.

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THE IMPORTANCE OF BREAST SELF-EXAMINATION AS A DIAGNOSTIC METHOD OF BREAST CANCER

A importância do autoexame como método diagnóstico do câncer de mama

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ABSTRACT

Method: An observational, retrospective, descriptive and cross - sectional study was carried out with data collected from Clínica Basegio, Brazil. The objective of this study was to analyze the importance of breast self-examination (BSE) as a diagnostic method for breast cancer in Passo Fundo, Rio Grande do Sul. A total of 320 patient records were selected from 1987 to 2017, among which 14 were excluded due to insufficient information. Results: BSE accounted for 48% of breast cancer diagnoses, followed by mammography and ultrasound. Imaging methods proved to be more effective in diagnosing early stage disease, while BSE detected more advanced tumors. This data was based on the histological characteristics of the tumors, with a significant difference ($p<0.05$) between tumor size and lymph node involvement when compared to BSE and imaging methods. Thus, the survival of the patients diagnosed by mammography and ultrasound was significantly higher than the patients diagnosed by BSE. Conclusion: Evidence from this retrospective study suggests that BSE is the prevalent diagnostic method for breast cancer in the State of Rio Grande do Sul. Despite detecting tumors in advanced stages, it is still a fundamental method within the Brazilian reality.

KEYWORDS: Breast cancer; self-examination; survival; mammography; ultrasound.

RESUMO

Método: Estudo observacional, retrospectivo, descritivo e transversal, com dados coletados na Clínica Basegio, Brasil. O objetivo deste estudo foi analisar a importância do autoexame das mamas (AEM) como método diagnóstico para o câncer de mama em Passo Fundo, Rio Grande do Sul. Um total de 320 registros de pacientes foram selecionados de 1987 a 2017, dos quais 14 foram excluídos devido a informações insuficientes. Resultados: O AEM foi responsável por 48% dos diagnósticos de câncer de mama, seguido pela mamografia e ultrassonografia. Os métodos de imagem mostraram-se mais eficazes no diagnóstico de doença em estágio inicial, enquanto o AEM detectou tumores mais avançados. Esses dados foram baseados nas características histológicas dos tumores, com diferença significativa ($p<0,05$) entre o tamanho do tumor e o comprometimento linfonodal quando comparados aos métodos de AEM e de imagem. Assim, a sobrevida dos pacientes diagnosticados por mamografia e ultrassonografia foi significativamente maior que a de pacientes diagnosticados por AEM. Conclusão: Evidências deste estudo retrospectivo sugerem que o AEM é o método diagnóstico prevalente para o câncer de mama no Estado do Rio Grande do Sul. Apesar de detectar tumores em estágios avançados, ainda é um método fundamental dentro da realidade brasileira.

PALAVRAS-CHAVE: neoplasias de mama; autoexame; sobrevivência (saúde pública); mamografia; ultrassonografia mamária.

INTRODUCTION

Breast cancer is the most common malignant cancer among women in Brazil and the world, excluding cases of non-melanoma skin cancer, and corresponds to 25% of cases of malignant cancers diagnosed each year[1]. The distribution in Brazil shows large regional differences, with higher rates of incidence and mortality in the Southeast and Southern regions and lower rates in the Northern and Northeast regions.

The disease is related to hereditary and environmental factors, and is sporadic in most cases. Its incidence is related to the control of risk factors, early diagnosis and appropriate treatment[2]. Breast changes are detectable during the physical examination performed by both the patient and the doctor, as well as by imaging tests such as mammography (MMG) or ultrasound (US), which are also tools used for its detection.

In breast self-examination (BSE), the patient observes and palpates their own breasts and accessory anatomical structures, in order to detect changes or abnormalities that may indicate the presence of a cancer. During the palpation of the breasts and adjacent structures (nipples, areolas and axillas), lymph nodes and condensations that are also suggestive of neoplasias can be noticed: reduced mobility/movement, adhered, hard and painless.

MMG allows for early detection of changes. According to the National Cancer Institute (NCI), MMG should be performed at the 50 to 69 year age group for people without a history of breast cancer in the family, with an interval of 1 to 2 years between the exams. For those with a history of cancer the recommendation is to start from 35 years of age[3].

Two randomized trials, one conducted in Russia[4] and another in China[5], compared the performance of BSE as an early diagnosis strategy in relation to non-intervention. The studies analyzed approximately 390,000 women and did not find statistically significant differences between the groups, mainly regarding mortality. However, due to epidemiological, economic and cultural differences, these studies can not be applied to the Brazilian reality.

Therefore, it is necessary to investigate the subject considering the Brazilian reality. This article offers support to ratify the importance of BSE as a diagnostic method.

The aim of the study was to compare the available methods for the diagnosis of breast cancer by means of the clinical data collection of patients from the northern region of the Rio Grande do Sul State and to evaluate the importance of BSE in the detection of breast cancer, mainly in aspects related to the prognosis.

METHOD

Population, sample and data collection

An observational, retrospective, cross-sectional study based on the analysis of medical records of patients treated at Clínica Basegio, located in the city of Passo Fundo in Rio Grande do Sul.

The data collection was based on the completion of a questionnaire prepared by the research team, which addressed aspects relevant to the clinic and the patients diagnosis. The questionnaire included aspects such as gender, age at diagnosis, diagnosis, staging, axillary status, surgery (included type of surgery performed), disease free interval, recurrence and survival.

The medical records were randomly chosen from more than 3,000 cases treated in the clinic from 1986 to 2017. The study included 320 randomized files, 14 of which were excluded for not containing complete data which was required to fill out the questionnaire , as well as cases whose patient outcome was unknown until data collection was completed. The final sample of the study consisted of 306 patients. Data were collected by the team between December 2017 and May 2018.

The classification used for data in relation to staging was: tumor size, axillary lymph nodes and metastases, from the seventh edition of the American Joint Committee on Cancer (AJCC).

Statistical analysis

The data collected from the questionnaire were tabulated in the Excel software (Office Plus 2013, Microsoft, Redmond, WA, USA) and in the SPSS program, version 18.0 (SPSS Inc., Chicago, IL, USA) for further analysis. Quantitative variables were demonstrated as mean and standard deviation, while frequency and percentage were used for qualitative values.

In order to verify the associations between the variables, the following tests were used: Kruskal Wallis test (for comparison of means in more than one category) and Mann-Whitney test (for comparison of means between two categories). The [Symbol]^2 test or the Fisher exact test were used to compare categories between groups. Survival analysis was performed using the Kaplan-Meier method. For all statistical analyzes, the level of significance was 5% ($p < 0.05$).

RESULTS

The study initially had 320 records to be analyzed. However, due to the fact that some were incomplete, 14 questionaries excluded. Finally, 306 medical records were included in the study. Among these, 304 were women and two were men. The diagnostic method prevailed as follows (Table 1): 48% of the sample detected the malignant lesion using BSE, while 52% did so with other diagnostic forms, including MMG, US and MRI (imaging methods).

For didactic purposes the diagnostic method with the variables (age, disease free interval, histological type, tumor size, lymph node involvement, surgical treatment, recurrence and survival) was analyzed dichotomously: BSE versus imaging methods.

The main age of patients who used BSE as a diagnostic method was 54.22 ± 13.76, and more than 30% were in the 60+ age group

(Figure 1). The avarage of the patients who used other diagnostic forms was 53.08 ± 12.33. No differences were found between the means (p = 0.678). The disease-free interval of patients diagnosed by BES in years was 6.82 ± 4.96, with little divergence when compared to other diagnostic methods, such as MMG and US, which obtained a mean of 7 ± 3.38 years. No significant difference was found (p = 0.487).

Nine different histological types were computed to compose the study sample. Based on that, four histological types of higher prevalence were considered. The most prevalent histological type detected by BSE was infiltrating ductal carcinoma (108/147), followed by other histological types (19/147), infiltrating lobular carcinoma (15/147) and ductal carcinoma *in situ* (5/147).

Regarding tumor size, there was a significant difference (p <0.001) between the main value diagnosed by BSE and the

other diagnostic methods. The other methods were able to identify smaller tumors than BSE, which detected mainly T2 (61/147), followed by T1 (52/147), T3 (19/147), T4 (12/147) and Tis (3/14), while the order of prevalence by other diagnostic methods was: T1 (80/159), T2 (45/159), Tis (21/159), T3 (12/159) and T4 (1/159), according to Figure 2.

The same pattern was found when the lymph node involvement was analyzed, i.e, the imaging tests obtained a lower percentage of lymph node involvement than the tumors diagnosed by BSE. In the group of patients who detected the lesion using BSE (147), 42% had some lymph node involvement. In the group of patients using other diagnostic methods (159), only 27% had lymph node involvement.

Regarding recurrence, only 76 patients presented recurrence (24.8%): 24 patients had local recurrence and 52 (68.4%) distant recurrence. Among the total number of patients with recurrence, 50 had initially discovered the tumor by BSE (65.8%).

Among the 300 patients who underwent surgical treatment, 169 underwent conservative surgery, with excision of the affected quadrant and lymph nodes, which corresponds to 55.2% of the total. Among these, 70 were diagnosed by BSE (41.1%). The remaining 131 patients underwent radical surgery, corresponding to 42.8%. Among these, 73 (51.7%) were identified by BSE, while 58 (44.3%) were identified by other methods.

Upon analyzing the survival in three groups (survival less than 5 years, between 5 and 10 years and over 10 years) there was a significant difference in the test [Symbol]^2, with a result

Table 1. Diagnostic method of breast cancer of patients, in four categories.

Diagnostic method	Frequency	Percentage	Valid Percentage	Cumulative percentage
BSE	147	48.0	48.0	48.0
Others	10	3.3	3.3	51.3
MMG	134	43.8	43.8	95.1
US	15	4.9	4.9	100.0
Total	306	100.0	100.0	

BSE: breast self-exmaination ; MMG: mammography ; US: ultrassound.
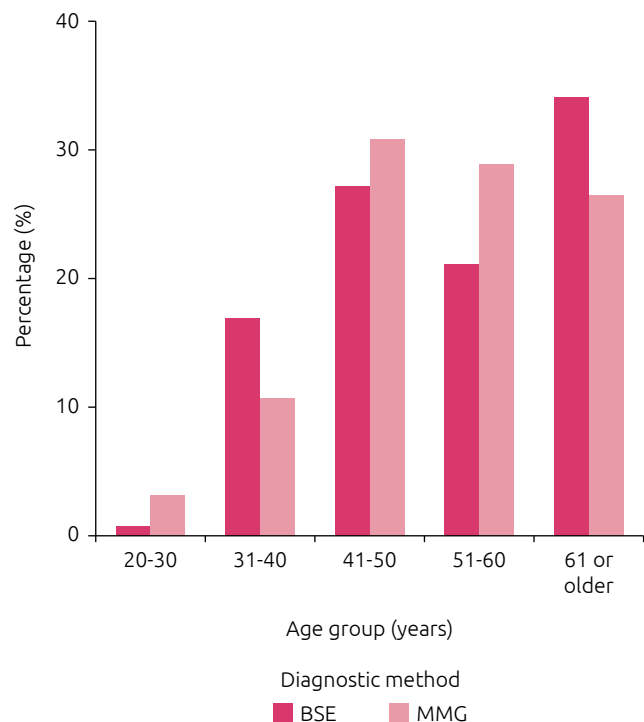
BSE : Breast self-examination; MMG: mammograph.
Figure 1. Relation of detected cases.
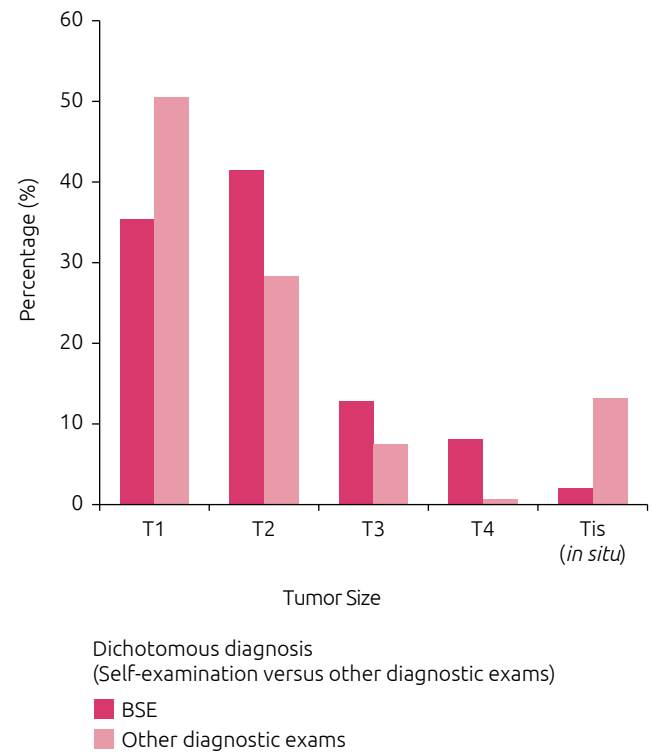
Figure 2. Relation of tumor size.

of 0.004. The groups that survived the most had their primary diagnosis performed primarily by MMG, followed by US.

The survival time was statistically (p <0.001) higher among study participants who had the first diagnosis performed by imaging exams, such as MMG and US, being 23.96 years old, with a 95% confidence interval (95% CI) %) 22.72-25.21; compared to the group with BSE as the initial diagnosis, being 19.86 (95% CI: 17.80-2.90) years old (Figure 3).

DISCUSSION

The present study comprehensively compared the profile of the patients who detected the malignant lesion of the breast by BSE and other diagnostic forms, obtaining results compatible with those previously described in the literature, which will be discussed below.

Breast cancer occurs more often in women than in men, around a hundred times more[6], which was compatible with the sample. A significant percentage (48%) of the sample used BSE as a diagnostic method, giving it great importance in the detection of breast cancer in the Brazilian reality.

The average of the diagnosis for all methods was on 53 years, corroborating the risk of developing malignant breast cancer with advancing age, which increases considerably after 50 years[7]. In a study performed at the Hospital das Clinicas de Porto Alegre (HCPA), between 1972 and 2002, with an analysis of 1,607 cases,

Group (self-examintion versus other diagnostic exams)
- ⌐ Breast self-examination
- ⌐ Other forms-diagnostic exams
- + Self-examination-censored
- + Other forms/diagnostic exams-censored

Figure 3. Survival relationship in years.

a average similar to the present study was observed: 53 years at the time of diagnosis[8].

The predominant age group in BSE was 61 years, while the predominant age group for MMG was 41 to 50 years. In a country of continental dimensions, BSE is a valuable diagnostic method, even if such patients, if they had performed MMG regularly from the age of 40, could have an earlier diagnosis and a better prognosis[9].

It is known that today the most aggressive cancers affect young women, under 50, because of the higher prevalence of risk factors such as hormonal exposure, family history and behavioral and environmental factors. In addition, it is fundamental to know the histological profile of the tumor to analyze the severity of the disease, the treatment options and the prognosis[10-12].

When analyzing the cross-referenced data of this sample and linking it with the clinic of the cases, it is possible to notice that BSE was more prevalent only in histological types with worse prognosis, for example, infiltrating ductal carcinoma, which has the worst indices of malignancy, such as metastases, affected lymph nodes and recurrence[13]. Generally, when these tumors are identified by BSE they have already become pre-malignant lesions - such as comedocarcinoma ductal carcinoma *in situ* - and, in comparison to other diagnostic methods, are discovered when tumor sizes are larger, usually from T214.

The data represent the fundamental role of MMG in detecting smaller tumors with better prognosis (without compromised lymph nodes and less aggressive histological type) due to early diagnosis. However, it does not exclude or decrease the 48% of the cases diagnosed by BSE in this study, which is still a fundamental method.

This high percentage is in line with the guidelines provided in the Ministry of Health's Guideline on Early Detection of Breast Cancer[15]. BSE is a considerable practice not only because of its high percentage, but it gains argumentative force when analyzing the socioeconomic characteristics of the patients. Despite being a growing practice[16], MMG in Brazil still fails to reach all the women who need the exam, either because they are unaware of the importance of self-care or the centralization of mammography devices in the reality of the Unified Health System[17]. Not encouraging the practice of BSE is limiting an easy-to-access, low-cost and affirming tool for the women and their bodies.

Conservative surgical treatment consists of quadrantectomy with lymphadenectomy (when indicated, a study of the sentinel lymph node is always performed) and was predominant in the majority of the cases of this study, around 55.2%. The result obtained is similar to that found in the study perfofrmed at the *Instituto de Mama* in Ubá, Minas Gerais, between 2001 and 2014, with an analysis of 647 patients, in which 67% of the patients underwent conservative surgery while only 33% underwent mastectomy[18].
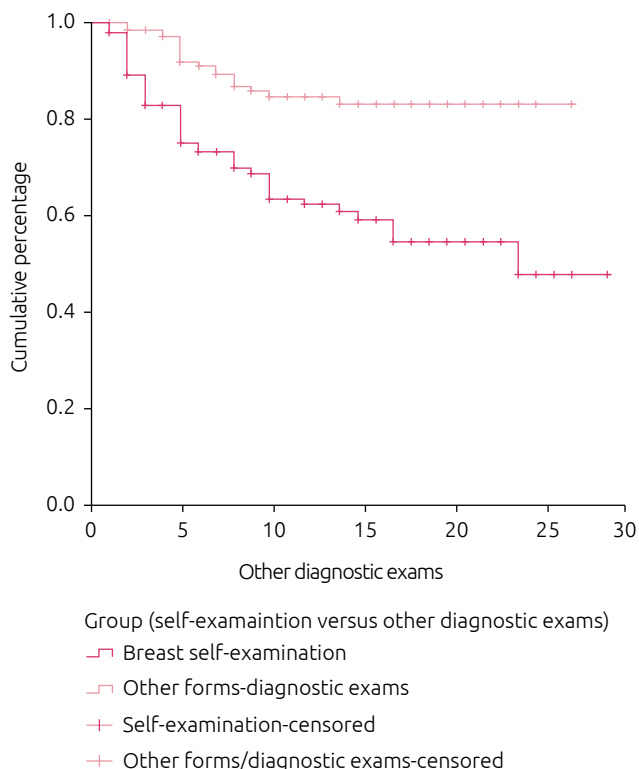
In the present study, it was observed that tumors that were at an advanced stage were most often diagnosed by BSE, in contrast to the other diagnostic methods (US, MMG, MRI), which together resulted in 44.7%[19] . According to a study conducted by Malmgren et al.[20], in the United States, in 2012, with an analysis of 2,579 cases, the individuals diagnosed by BSE did so in late stages of the disease, requiring radical mastectomy as a treatment

The vast majority of patients did not present recurrence and, among the few that presented, there was a predominance of BSE. Considering that most of the malignancies diagnosed by BSE were in a more advanced stage, there is an increase in the likelihood of recurrence in these patients, even with the attempt of radical or conservative surgical cure, although, in a study published in the New England Journal of Medicine , this difference between the presence or absence of recurrence depends not on the type of surgery or the initial diagnostic method of the tumor, but on the type of therapy associated with surgery (such as hormone and chemotherapy) in cases of invasive disease, which could be better analyzed in later studies[21]. In the present study, those who had an initial diagnosis by BSE had a higher prevalence of recurrence compared to those diagnosed by other methods. However, no studies were found to corroborate this analysis.

According to Vicini et al.[22], in a survey conducted in 2003, 4 to 20% of patients with breast cancer presented local recurrence, which is confirmed by the present study, with 8%. On the other hand, regarding this analysis, local recurrence is related to the type of surgery - the conservative ones have a higher incidence of recurrence than the radical ones -, and the occurrence or absence of distant disease[23]. Nevertheless, based on data analysis, there was no statistical difference between the type of recurrence and diagnostic form.

The data found in relation to the greater survival in the group whose diagnosis was first performed by imaging methods (US and MMG) corroborates with the literature. Some studies describe the use of MMG and its association with a reduction in mortality, since it has the capacity to diagnose neoplastic lesions in the early stages, before they are large enough to be palpable and, therefore, an excellent examination for secondary prevention. The routine use of this test is, therefore, fundamental in the diagnosis of breast cancer in women over 50 years of age[19,24,25].

The practice of BSE has been a subject of debate. It was mainly advocated in the 1950s when there were no other effective methods for the early and asymptomatic diagnosis of nodules, making late diagnosis of breast neoplasms the most common pattern. Unlike MMG, BSE was not able to reduce breast cancer mortality rates in two large studies conducted in China and Russia. In addition, BSE considerably increased the number of unnecessary biopsies for benign nodules. BSE may not identify the nodules because they are very small or because they are performed inadequately, resulting in a false sense of security[19,26-2]

The limitation of this analysis is due to it being a retrospective study, which is susceptible to errors in medical records, as well as not having an active follow-up in order to know which patients died due to cancer. In addition, the database used to conduct the research came from a breast surgery clinic. For this reason, many patients with more advanced stage cancers and with no possibility of surgical treatment are underestimated in the case-by-case analysis.

It is now known that MMG is the most important imaging method for the early diagnosis of breast cancer, since it is the only one capable of decreasing the mortality related to the disease. Therefore, BSE is not recommended as the only screening method and its joint performance with MMG is still controversial.

The results obtained in this study demonstrate that this practice is still prevalent in the population, and most frequent in the studied group. BSE usually detects advanced disease, which calls into question the incentive of this practice. In spite of this, we still agree with the importance of such method in our reality, not in any way dispensing with the periodic accomplishment of MMG.

Women should be encouraged to take abnormalities found at the EMA to the doctor's office and they should be instructed to perform the test in order to differentiate what is abnormal and to understand that BSE should not be used as a substitute for MMG.

ACKNOWLEDGMENTS

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PROFILE OF CARE IN YOUNG WOMEN WITH BREAST CANCER IN AMAZONAS: 11 YEARS STUDY

Perfil de atendimento em mulheres jovens com câncer de mama no Amazonas: estudo de 11 anos

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ABSTRACT

A cross-sectional, retrospective cohort study was carried out to describe the profile of breast cancer patients aged 40 years or less diagnosed and treated at the CECON/FCECON Foundation from 2003 to 2013. The following were evaluated: age, staging, place of origin and diagnostic accuracy, through search of records in patients' records. Data were computed in a database and analyzed through descriptive statistics. There were 211 patients under 40 years with breast cancer in the study period, representing 9.83%. The most affected age group was between 35 and 40 years. Regarding clinical staging, 57 cases were at stage IIA at diagnosis. About the method of screening, 71 patients performed it through clinical examination or self-examination and, in relation to the provenance, 48 cases were from other states. It is necessary to improve diagnosis in this age group and that the institutional care be directed to the patients of their original states.

KEYWORDS: Breast cancer; epidemiology; early diagnosis.

RESUMO

Um estudo de coorte retrospectivo, de corte transversal, foi realizado para descrever o perfil de pacientes com câncer de mama com 40 anos ou menos diagnosticados e tratados na Fundação CECON/FCECON de 2003 a 2013. Foram avaliados: idade, estadiamento, local de origem e acurácia diagnóstica, através da busca de registros nos prontuários dos pacientes. Os dados foram computados em um banco de dados e analisados por meio de análise estatística descritiva. Havia 211 pacientes com menos de 40 anos com câncer de mama no período do estudo, representando 9,83%. A faixa etária mais afetada foi entre 35 e 40 anos. Em relação ao estadiamento clínico, 57 casos estavam no estágio IIA no momento do diagnóstico. Sobre o método de triagem, 71 pacientes realizaram o exame clínico ou o autoexame, e em relação à procedência, 48 casos foram de outros estados. É necessário melhorar o diagnóstico nessa faixa etária e direcionar o cuidado institucional seja aos pacientes de seus estados originais.

PALAVRAS-CHAVE: Câncer de mama; epidemiologia; diagnóstico precoce.

INTRODUCTION

Young women are more vulnerable to late diagnosis due to the lack of mammographic screening actions that they do not do because of the difficulty of interpreting mammography taking into account the high breast density that these women present[1-5].

These women have an unfavorable prognosis in relation to older women. The reason for this difference is quite complex and related to tumor biology and delayed diagnosis, once they are diagnosed at a more advanced stage, with palpable tumors, greater lymph node involvement and an extensive intraductal component, besides having a greater possibility of not responding to endocrine treatment[3,6-11].

In this study, we compared the results obtained and presented them in Figure 1. The sensitivity of the clinical examination for cancer diagnosis in young women is very variable, since the malignant nodule may have a misinterpretation that delays its identification and worsen its prognosis. The diagnosis of these patients requires an extremely careful approach. These findings point to the importance of breast examination in the routine visit to the health professional, which is undoubtedly performed prior to the start of mammography screening[12].

Age, as a prognostic factor, is important in mammary neoplasia, because if the diagnosis is performed early it can be cured by performing a more aggressive treatment, due to recurrence and low survival, which are common to this group[9,13].

Breast carcinoma is uncommon among young women, accounting for 5 to 7% of cases in some series. Defined by several authors such as those that develop before 30, 35, 40, 45 or even 50 years, it presents with worse prognosis, since its diagnosis is made when the patient is symptomatic and, therefore, has already evolved to a more advanced stage of the disease. As a result, mortality rate was significantly higher in the postmenopausal group[2,3,14] than in the postmenopausal period. The greater vulnerability of young women to advanced diagnosis is justified by the lack of tracking actions and the difficulty in reading and interpreting mammographic results due to high breast density. Another factor that may contribute is the false perception, by many health professionals, that young women are not at risk of developing cancer, devaluing early signs and symptoms of the disease[3].

The objective of this study was to describe the prevalence of breast cancer in women under 40 years from 2003 to 2013 at the CECON Foundation and to analyze the sensitivity of diagnostic methods, clinical staging and patients' origin.

METHOD

Observational epidemiological study, descriptive of a cross-sectional cohort, diagnosis and retrospective cohort of the patients attended at the Oncology Control Center Foundation of Amazonas (FCECON), in Manaus, aged under 40 years, with breast cancer in the period of 2003-2013. Variables assessed: age, histological type, diagnostic method and staging.

The study was appraised and approved by the CECON Foundation's Research Ethics Committee on Human Beings with the CAAE number 39812114.7.0000.0004.

The Term of Free and Informed Consent (TCLE) for accessible women was used and waiver was requested for non-accessible women. Due to these cases, the Term of Commitment of Data Use (TCUD) was presented, in which the researchers committed themselves to data's secrecy and confidentiality.

The inclusion criterion was women diagnosed with primary breast cancer aged 40 years or less treated at the CECON Foundation from January 2003 to December 2013.

Women who presented medical records without the information necessary for the study were excluded.

RESULTS

Analyzing the variable age, it was observed that the youngest woman was 21 at the time of diagnosis and the oldest 40 years; the median age was 37 years, with a predominance of women in the age group of 35–40 years (67.8%), the age group with the least involvement was between 21 and 25, equivalent to 2.8% of the sample (Figure 1).

Patients treated from 2003 to 2013 were identified as coming from Manaus, Amazonas' capital, from other states and even from other countries. The presence of patients from other states happens because these are geographically close to Manaus. In relation to other countries, it has been observed that, in recent years, refugees from Haiti and patients from Venezuela have come to the Amazon capital.

A total of 211 patients were attended at the CECON Foundation, of whom only 195 had a medical record from their origin. In this period, 53.8% were from Manaus, 24.6% from other states, 21% from the interior of Amazonas and 0.5% were from other countries (Table 1).

Among the 211 women diagnosed with breast cancer, 95 (45%) underwent breast ultrasonography and 108 (51.2%) underwent mammography. Regarding mammography, BIRADS II classification
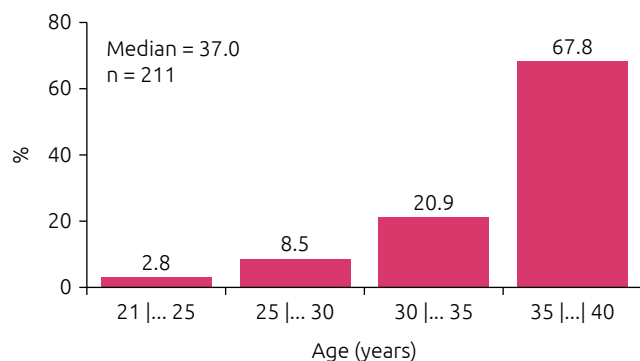

Figure 1. Distribution according to the age of women with breast cancer under 40 years old attended at Oncology Control Center Foundation of Amazonas (FCECON), 2003–2013, Manaus (AM), Brazil.

occurred in 33 cases (30.6%), BIRADS IV in 25.9% and BIRADS V in 25.9% of the cases (Table 2).

Between the 95 women who underwent ultrasound, 46.3% presented BIRADS IV classification and 21.1% presented BIRADS V.

Among the 108 patients who underwent mammography, there was an association with ultrasound in 66.3% of the cases. From all 211 patients evaluated, 71 (33.6%) had not performed any type of imaging; their diagnosis was made by clinical or self-examination, according to Table 3.

Although there was no statistically significant difference, ultrasound showed a sensitivity of 67.4% for breast cancer diagnosis and mammography in only 57.4% (Table 4).

Table 1. Distribution according to the origin of women with breast cancer under 40 years attended at Oncology Control Center Foundation of Amazonas (FCECON), 2003–2013, Manaus (AM), Brazil.

Variables	f_i	%
Place of origin (n=195)		
Manaus	105	53,8
State of Amazonas	41	21,0
Other states	48	24,6
Other countries	1	0,5

f_i: frequency.

Table 2. Distribution of women with breast cancer under 40 years in relation to ultrasound and mammography treated at Oncology Control Center Foundation of Amazonas (FCECON), 2003–2013, Manaus (AM), Brazil.

Variables	f_i	%
Ultrasound (n=211)	95	45,0
Classification		
I	8	8,4
II	10	10,5
III	13	13,7
IV	44	46,3
V	20	21,1
Average±DP	3,6±1,2	
Mammography (n=211)	108	51,2
Classification		
00	6	5,6
I	5	4,6
II	33	30,6
III	8	7,4
IV	28	25,9
V	28	25,9
Average±DP	3,2 ± 1,4	

f_i: frequency; DP: standard deviation.

DISCUSSION

Foxcroft et al.[15], in a retrospective study, assessed 239 patients under 40 years, and the most affected age group was that between 35 and 39 years old (66.5%), as in our sample, in which this group represented 67.8% of the patients.

Bharat et al.[16], 3,596 patients from the 1998–2006 period treated for breast cancer in St. Louis, USA were evaluated. They were aged under 40 years in 9.6% of the cases and 90.4% were over 40 years. In our case, this group represented 9.83%.

In the present study, 53.8% of the patients were from Manaus, 21.0% were from the interior of Amazonas, 24.6% were from other states in the northern region and 0.5% from other countries. The care of patients from other states at FCECON occurs due to the geography of the region, because due to its continental dimensions, the institution is often closer to patients than the ones in their own state of origin. This creates a significant financial cost for Amazon that is not passed on to other states. In addition, this migration overloads the service and increases the difficulty of improving access from early diagnosis to treatment, distancing the time between these two steps. In this way, FCECON presents a statistics of care and diagnosis of patients from the state of Amazonas and also from the rest of the northern region.

Table 3. Distribution according to the ultrasound frequency in relation to mammography of women with breast cancer under 40 years attended at Oncology Control Center Foundation of Amazonas (FCECON), 2003–2013, Manaus (AM), Brazil.

Mammography	Ultrasound				Total
	Yes		No		
	f_i	%	f_i	%	
Yes	63	66,3	45	38,8	108
No	32	33,7	71	61,2	103
Total	95	45,0	116	55,0	211

f_i: frequency.

Table 4. Distribution according to the sensitivity of the ultrasound and mammography examinations of women with breast cancer under 40 years attended at Oncology Control Center Foundation of Amazonas (FCECON), 2003–2013, Manaus (AM), Brazil.

Variables	f_i	%	95%IC
Ultrasound (n=95)			
Class 4 and 5	64	67,4	57,0–76,6
Class 1, 2 and 3	31	32,6	23,4–43,0
Mammography (n=108)			
Class 0, 4 and 5	62	57,4	47,5–66,9
Class 1, 2 and 3	46	42,6	33,1–52,5

f_i: frequency; 95%IC%: confidence interval at the level of 95%.

Regarding clinical staging, 27.5% of the cases were staged as IIA, followed by IIIB (21.3%) and stage IV (2.4%), demonstrating that diagnosis was made late. This distribution demonstrates that women are already diagnosed at advanced stages of the disease, making treatment even more challenging.

In the case of Pinheiro et al.[9], the diagnosis was predominantly in the IIA. The IIIB stage was considered as an advanced carcinoma in 62.8% of the patients, and distant metastasis occurred in 9.7% of the cases.

In a retrospective study with 507 women carried out by Thangjam et al.[5], 160 were under the age of 40 years (31.56%) and 347 were over 40 years old (68.44%). Stage III was the most common (47%), followed by stage II (34%) and stage I occurred only in 11% of the patients.

In the present study, mammography was effective in the diagnosis of mammary neoplasia with the category of classification BIRADS IV in 25.9% and class V in 25.9%. Mammography was not effective in this diagnosis in 40.8 % due to class 0 in 5.6%, class I in 4.6% and class II in 30.6%, demonstrating the low sensitivity of the method.

Ultrasonography can detect lesions that mammography is not capable due to breast density. Ultrasonography identifies lesions 95.7% more than the intraductal microcalcifications according to the data of An et al.[17], agreeing with the findings of this study, which demonstrated that ultrasound is more effective than mammography in young patients.

In the series by Yankaskas et al.[14], the comparison between younger and older women was made. Specificity was lower in women between 18 and 39 years and sensitivity was lower (76.5%) in younger women. The detection rate between the ages of 18 and 39 was 1.7% per 1,000 mammograms and 2.3–1,000 / mammograms in the age group of 40–44 years. In women between 45 and 49 years the rate was of 4.3 per 1,000 / mammograms. The poor performance of mammography in these patients is due to the breast density that masks the tumors.

Partridge et al.[2] evaluated the effect of age on delayed diagnosis and staging of breast carcinoma, and identified that mammography diagnosed women under 40 years in only 10.4% of the cases and women above 40 years in 48%. In this series, the diagnosis was made by self-examination in 39.1% of the patients under 40 years. These data are similar to those found in the present study, where patients identified the lesions in 33.6% without having performed imaging tests, reinforcing the association of delayed diagnosis and advanced stage of the disease.

According to the recommendation of the Brazilian Federation of Associations of Gynecology and Obstetrics (FEBRASGO) and the Brazilian Society of Mastology (SBM), women under 40 should not perform mammography and ultrasonography as a screening method. For high-risk patients, it is recommended that the screening strategy be individualized. The expected benefits should always be weighed against the risks involved, noting that the young breast may be more sensitive to the radiation's carcinogenic effect. It is considered that not only the sensitivity of mammography is decreased by the dense breast, but the dose of radiation dispensed by the mammograph in these cases is larger[18].

There are reasons for the adverse prognosis of breast carcinoma in young women. Without doubt, the biological tumor's characteristics and the delay in diagnosis are the main causes for this thought. In a retrospective study between 2007 and 2014, Telfah et al.[10] identified 160 women with breast cancer below and above 40 years, in which the median age was 35 years. This study demonstrated that the delay in diagnosing young women is around 8.35 weeks and in older women around 7.44 weeks. It is believed that this delay occurs due to the breast density and the low probability of cancer in young women.

In a retrospective study with 628 women under 40 years of age in the period of 1996 to 2008 in Massachusetts, with the median age of 37 years, the disease was detected by auto examination in 71% of the cases, by mammography in 24% and resonance in 1%. The mean size of the tumors was between 1 and 2 cm and the carcinoma in situ diagnosed only in 19%[19].

CONCLUSION

FCECON service not only demonstrates the reality of the Amazon, but also reflects the reality of the North region, once 24.6% of the patients come from other states. Having this, it should be considered that institutional care should be directed to patients in their State of origin, and it is necessary to improve diagnosis in this age group.

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IS THERE A SAFE TUMOR SIZE FOR IDENTIFICATION OF BREAST CARCINOMA WITHOUT AXILLARY NODE METASTASIS?

Há um tamanho seguro para a identificação do carcinoma mamário sem metástase linfonodal?

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ABSTRACT

Objective: To evaluate the rate of absence of axillary pathological involvement in patients with clinically negative axilla, submitted to axillary lymphadenectomy (AL). **Method:** Retrospective longitudinal study, which clinically evaluated patients without axillary metastasis (cN0), who underwent oncologic treatment from 1998 to 2001. Patients were selected at clinical stage I to III. The axillary pathological impairment ratio was correlated with tumor size and clinical stage T and TNM. We also evaluated the locoregional and axillary (local) recurrences. **Results:** 519 clinically cN0 patients were selected. All were submitted to AL, with a mean of 18 lymph nodes dissected and 3.2 compromised. The axillary metastatic rate was 47.2%. Tumor size and clinical stage were associated with the presence of axillary lymph node metastasis (p<0.001). The axillary involvement was of 78.6% for tumors between 6.1 to 8 cm, and of 100% for tumors larger than 8.1 cm. Forty patients were T4-TNM, where the impairment rate was 57.5%. The specific survival at 120 months was 71.1%, with locoregional recurrence rate of 6.9% (n=36) and local rate of 0.4% (n=2). **Conclusion:** In patients submitted to axillary lymphadenectomy, the axillary recurrence was extremely low. There are patients with tumors greater than 5 cm, smaller than 8 cm, and selected T4-TNM without metastasis in axilla. Further studies are necessary to evaluate sentinel lymph node dissection in this selected group, but it is unacceptable for tumors larger than 8.1 cm.

KEYWORDS: breast neoplasms; sentinel lymph node biopsy; lymph node excision; recurrence; neoplasm recurrence, local.

RESUMO

Objetivo: Avaliar a taxa de ausência de comprometimento anatomopatológico axilar em pacientes com axila clinicamente negativa, submetidas à linfadenectomia axilar (LA). **Método:** Estudo retrospectivo longitudinal que avaliou pacientes clinicamente com ausência de metástase axilar (N0), submetidas a tratamento oncológico no período de 1998 a 2001. Selecionaram-se pacientes no estádio clínico de I a III. Avaliou-se a relação entre a taxa de comprometimento anatomopatológico axilar, o tamanho do tumor e o estádio clínico T e TNM. Avaliou-se também o risco de recidiva locorregional (RLR) e de recidiva local axilar (RLA). **Resultados:** 519 pacientes clinicamente N0 foram selecionadas. Todas foram submetidas à LA, com o número médio de 18 linfonodos dissecados e 3,2 comprometidos. A taxa de doença metastática axilar foi de 47,2%. O tamanho do tumor e o estádio clínico estiveram associados à presença de metástase linfonodal axilar (p<0.001). Tumores de 6,1 a 8 cm apresentaram 78,6% de comprometimento, e em tumores maiores que 8,1 cm essa taxa foi de 100%. Quarenta pacientes eram T4-TNM, nos quais a taxa de comprometimento foi de 57,5%. A sobrevida específica aos 120 meses foi de 71,1%, a taxa de RLR foi de 6,9% (n=36) e a RLA de 0,4% (n=2). **Conclusão:** Em pacientes submetidas à linfadenectomia axilar, a taxa de recorrência axilar foi extremamente baixa. Há pacientes com tumores maiores que 5 cm e menores que 8 cm, T4-TNM, em que a axila se mostrou sem doença metastática axilar. Fazem-se necessários mais estudos prospectivos para avaliar a dissecção do linfonodo sentinela em casos selecionados de tumores T3 e T4 clínico, sendo a dissecção inaceitável para tumores com tamanho superior a 8,1 cm.

PALAVRAS-CHAVE: neoplasia da mama; biópsia de linfonodo sentinela; excisão de linfonodo; recidiva; recidiva local de neoplasia.

INTRODUCTION

Breast cancer is the most prevalent neoplasm in females and is a serious public health problem worldwide, as approximately 1.38 million new cases are diagnosed per year. Moreover, breast cancer has an increasing mortality rate, of which 60% occur in developing countries[1].

For a long time, axillary lymphadenectomy (AL) was the standard treatment for breast cancer, since 97% of the drainage is axillary[2]. The NSABP-04 clinical trial demonstrated that the conventional AL alone did not provide a survival benefit[3]. Many patients without axillary metastasis were subjected to AL, which led to the sentinel lymph node concept[4]. Sentinel lymph node biopsy (SLNB) can accurately predict axillary status[5,6]. The NSABP B-32 trial showed a false-negative rate of up to 9.8% for sentinel lymph nodes, and even with a high false-negative rate, axillary recurrence after metastasis-negative SLNB was of only 0.25% after an average follow-up period of 21 months[7].

Thus, over time, SLNB was considered the best breast cancer axillary management in patients with clinically N0 axillary nodes, and was initially proposed for tumors smaller than 3 cm and later for tumors up to 5 cm (T2-TNM), although studies of tumors that ranged from 3.1 to 5.0 cm were limited. The American Cancer Society considers SLNB acceptable for T1 and T2 tumors[8,9]. Estimates of SLNB accuracy based on tumor size suggest that, for primary lesions greater than 3.0 cm, this value reaches 96%. However, according to the literature, several isolated studies on the use of SLNB for T3 and T4 tumors without the use of neoadjuvant chemotherapy (NAC) have been reported[9-13].

Similarly, the N0 axillary node concept also became controversial since the performance of an ultrasound examination allowed questioning the clinical event, and it was observed that the ultrasound indicated disease in the axillary nodes of many clinically N0 patients who are often subjected to biopsy with positive results[14]. This finding has been reinforced by the diagnostic evaluation method (fine needle puncture or core biopsy)[15]. In fact, there is no defined cut-off point for morphological change or cortical lymph node thickening, and many patients who undergo puncture or core biopsy will not demonstrate axillary involvement[15,16].

Many initial contraindications to SLNB have become debatable and relative over the years[17]. Recently, this type of axillary surgical management has been increasingly associated with NAC. Many patients with locally advanced tumors are candidates for NAC, but a portion of them are clinically N0 prior to chemotherapy or become negative after NAC[18]. SLNB after NAC is feasible, but it is associated with a reasonably high rate of false-negative results, especially when three lymph nodes are resected. No study with a long follow-up period that has demonstrated the safety of this procedure with respect to local axillary recurrence has been published. Many patients who are diagnosed as N0 prior to NAC could be candidates for SLNB, and based on a good response to NAC, they would not be candidates for SLNB or AL after it. Those patients would avoid the confounding effects generated by their responses to NAC, which determine a tumor sub-stage; this in turn may lead to unnecessary AL[4,19].

Breast cancer is the most prevalent neoplasm in women, and thus, even if a procedure is performed in a select group of patients, the number of procedures will be high. The larger the tumor is, the greater the probability of regional lymph node involvement[13], but studies on the applicability of SLNB to T3 or T4 tumors are limited. In turn, studies that have evaluated the rate of metastatic disease in patients with clinically N0 axillary nodes in T3 or T4 tumors are also limited in number, and little information is available on the rate of axillary recurrence under these specific conditions. This justifies the need for additional studies on this subject, especially since in the pre-SLNB era, such patients were systematically subjected to AL. Axillary evaluation and treatment play a therapeutic role, but these processes are increasingly seen as part of clinical staging and not as treatments. This leads to increased questioning about the need for AL, and therefore justifies the present study.

MATERIALS AND METHODS

This retrospective, longitudinal study was based on a historical series of all clinical stage I to III patients with no clinical axillary lymph node disease (N0) who were treated at the Barretos Cancer Hospital (Hospital de Câncer de Barretos — HCB) from 1998 to 2001 and who were subjected to AL. This study was approved by the HCB's Research Ethics Committee under number 495/2011.

Out of 1,493 patients, those with a previous cancer diagnosis and those who received prior treatment were excluded. From the remaining 956 patients, those with clinical stage 0 and IV were excluded, like those patients whose tumor histologies were not classifiable by the TNM system. Next, from the 728 remaining patients, those who did not undergo AL and those with fewer than five lymph nodes dissected were excluded. Patients with occult primary tumors were excluded from the 670 patients who remained, which resulted in 652 patients. Out of these, 108 with clinical N0 disease who underwent NAC and 25 patients for whom information on tumor size was lacking were excluded, which resulted in the 519 cases composing the sample of the present study.

The rate of axillary lymph node involvement as a function of tumor size and T-TNM stage was evaluated (Table 1). The 7th edition of the TNM staging system was used.

All patients underwent adjuvant treatment (Table 2). Since this was a historical series, standard chemotherapy was used at that time (only 10.4% of the patients did not undergo chemotherapy), and most of the patients received an adjuvant regimen based on CMF (69.5%) or FAC (9.2%). At the time of the study, adjuvant tamoxifen was used for two years, but trastuzumab was not used. The indications for radiotherapy remained unchanged.
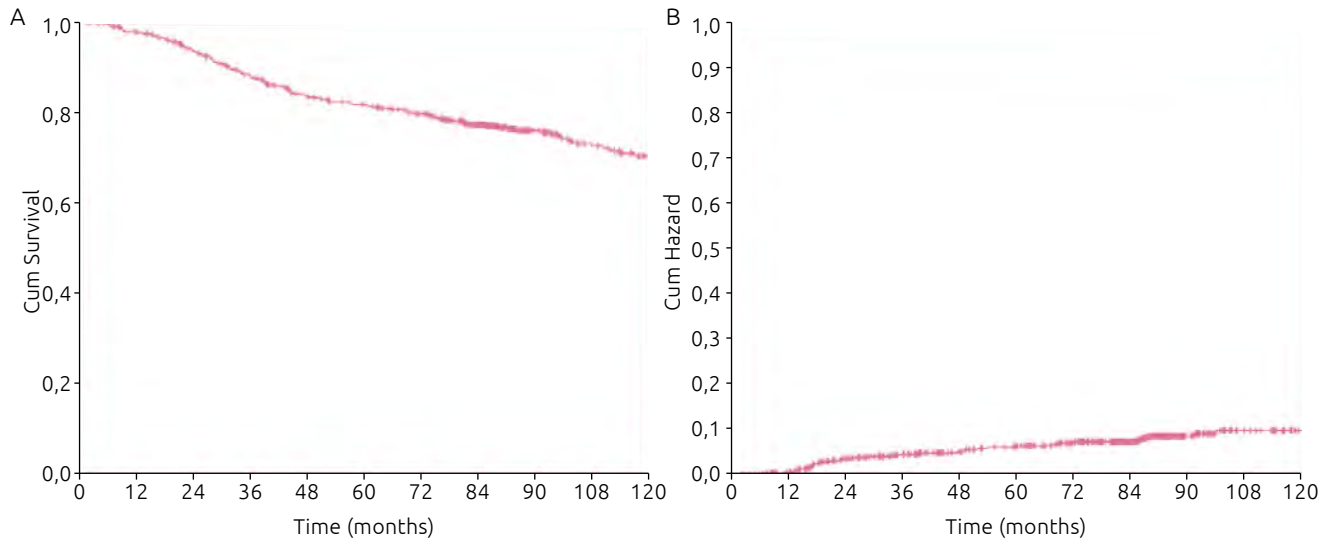
Figure 1. Results regarding follow-up time. (A) Cancer-specific survival; (B) hazard ratio for locoregional recurrence.

Table 1. Distribution of lymph node involvement according to tumor size and clinical stage.

	Category	Negative	Positive	Total	P
		n (%)	n (%)		
Size	0.1–1	23 (76.7)	7 (23.3)	30	
	1.1–2	74 (64.3)	41 (35.7)	115	
	2.2–3	90 (52.3)	82 (47.7)	172	
	3.1–4	51 (46.4)	59 (53.6)	110	
	4.1–5	21 (41.2)	30 (58.8)	51	
Segmental	5.1–6	12 (52.2)	11 (47.8)	23	<0.001
	6.1–7	2 (20.0)	8 (80.0)	10	
	7.1–8	1 (25.0)	3 (75.0)	4	
	8.1–9	0	2 (100)	2	
	9.1–10	0	2 (100)	2	
Size	0.1–3	187 (59.0)	130 (41.0)	317	
	3.1–5	72 (44.7)	89 (55.3)	161	
Grouped	5.1–6	12 (52.2)	11 (47.8)	23	<0.001
	6.1–8	3 (21.4)	11 (78.6)	14	
	8.1–10	0	4 (100)	4	
T-TNM Clinical	T1	92 (67.2)	45 (32.8)	137	
	T2	153 (49.5)	156 (50.5)	309	
Staging	T3	12 (36.4)	21 (63.6)	33	<0.001
	T4	17 (42.5)	23 (57.5)	40	
Subgroup	0.1–3	9 (69.2)	4 (30.8)	13	
	3.1–5	5 (26.3)	14 (73.7)	19	
	5.1–6	1 (50.0)	1 (50.0)	2	0.156
T4-TNM	6.1–8	2 (40.0)	3 (60.3)	5	
	8.1–10	0	1 (100)	1	

TNM: TNM 7th edition; T: tumor TMN.

Follow-up was assessed from the first until the last visit, and patients were considered to be lost of follow up if they did not return to the clinic at least two times, with the schedule time during 120 months. Cancer-specific survival and locoregional recurrence were also evaluated. Locoregional recurrence indicates recurrence in the chest wall, contralateral breast, supraclavicular fossa, or the ipsilateral or contralateral axilla. Axillary recurrence refers to the presence of axillary, retropectoral or axillary cavity disease, near the entrance of the subclavian artery.

Descriptive statistics were used to evaluate the results. Values with loss of information below 1% were reported and were excluded from the analysis. To evaluate the variables related to tumor size and lymph node positivity, the chi-square test was used. Survival was analyzed using Kaplan's and Meier's method, and the risk of recurrence was evaluated using hazard ratios; the log-rank method was used in both situations. Differences in which $p<0.05$ were considered significant. IBM SPSS for MAC version 20 was used for all statistical analyses.

Table 2. Characteristics of the treatment population.

Variable	Category	n	%
Pretreatment and staging			
Age	Up to 40	72	13.9
	40–69	367	70.7
	>70 years	80	15.4
TNM Clinical	I	88	17.1
Staging	II	320	62.0
	III	12	20.9
N-TNM Clinical	N0	274	52.8
Staging	N1	131	25.2
	N2	52	10.0
	N3	62	11.9
Treatment			
Surgery	Mastectomy	364	70.1
	Quadrantectomy	155	29.9
Chemotherapy*	Not performed	56	10.8
	Adjuvant	393	75.9
	Palliative	28	5.4
	Adjuvant and palliative	41	8.0
Hormone therapy*	Not performed	258	49.9
	Adjuvant	233	45.1
	Adjuvant and palliative	26	5.0
Radiotherapy	Not performed	30	5.8
	Adjuvant breast / axilla	329	63.4
	Adjuvant breast and fossa	170	32.8
	Recurrence	6	1.2
Follow-up			
Recurrence	Absent	480	93.0
Locoregional*	Present	36	6.9
Metastasis	Absent	383	73.8
	Present	136	26.2
Final status	DC	124	23.9
	DAS	31	6.0
	DWOO	10	1.9
	AWD	311	59.9
	AWOD	43	8.3

TNM: TNM 7th edition; N-TNM: TNM lymph node evaluation; *missing <1%; DC: death due to cancer; DAS: death due to associated disease; DWOO: death without observation; AWD: alive with disease; AWOD: alive without disease.

RESULTS

In all, 519 patients were evaluated. All patients underwent axillary lymphadenectomy; the mean number of dissected lymph nodes was 18 (range 7–49), and the mean number of lymph nodes involved was 3.2 (range 0–40). Overall, 47.2% of the patients were diagnosed with metastatic axillary disease. Table 1 shows the relationship between tumor size, T-TNM clinical stage and the presence of axillary metastatic disease. It was observed that the larger the tumor size, the higher the axillary metastatic disease rate. However, for tumors between 6.1 and 8.0 cm, this rate was 78.6%, while for tumors larger than 8.1 cm, this rate was 100% (Table 1).

Most of the patients were older than 40 years (86.1%) and had stage II or III disease (82.9%), but 52.8% of the patients had pathological N0 disease. Regarding the treatment performed, most patients underwent mastectomy (70.1%), while chemotherapy (75.9%), hormone therapy (50.1%), and radiotherapy (93.0%) were used as adjuvant therapies (Table 2).

The follow-up time spanned from January 1998 to October 2010, with a mean follow-up of 78.6 months (range 0.6–142 months). The percentage of patients considered to be lost of follow up was 5.4% (n=28); they had a median follow-up time of 37.7 months and data on locoregional recurrence of these patients were unavailable for only three patients. The cancer-specific survival was 81.4% at 60 months and was 71.1% at 120 months (Figure 1A).

At the end of the evaluation, 23.9% had died due to disease progression, 8.3% experienced recurrence after treatment, and 7.9% had died by another cause. During this period, 26.2% developed distant metastasis and 6.9% (36) developed locoregional recurrence (LRR). In the three patients who died, it was not possible to evaluate data regarding LRR. The mean time to LRR was 39.1 months (range 6.9–101.3 months). Figure 1B shows the hazard ratio for the LRR. The LRR (n=36) was evident in 66.7% (n=24) of the cases, and the main site of recurrence was chest wall (47.2%, n=17). The next most frequent was recurrence after quadrantectomy and in contralateral axilla (22.2%; n=8 each), contralateral breast, and ipsilateral and contralateral supraclavicular fossa

(11.1%, n=4 each). Ipsilateral axillary recurrence was observed in only 0.4% of all patients (5.6% of all local recurrences).

Of the two patients with local recurrence, both had triple-negative invasive ductal carcinoma and underwent mastectomy with AL; they also received 5,040 cGy radiotherapy and chemotherapy (12 CMF) and were followed-up. The first patient was primarily T2N0MO, had a tumor 3.5 cm in diameter and experienced recurrence in the chest wall, subclavian region and pectoral muscle at 17 months. The second patient was diagnosed as T3N1M0, had a tumor with 6.0 cm in diameter, and experienced retropectoral recurrence at 26 months.

DISCUSSION

In the past several years, the concept of clinically N0 (cN0) axillary nodes has been subjected to a greater debate since. SLNB for cN0 was first associated with AL for tumors lower than 3 cm and it was later extended for tumors under 5 cm. Now, SLNB is considered safety of tumors lower than 5cm; we also evaluated AL for T3 and T4 tumors, where we observed a considerable number of patients without axillary metastasis. This study gives bases for evaluating SLNB for T3 and T4 tumors, and probably, in the presence of pathological negative SLNB, AL can be avoided. Imaging exams can help our evaluation. Likewise, with the addition of imaging exams, especially axillary ultrasound, new parameters were added due to the improved characterization of lymph node shape, cortical thickening, and internal halo loss. These conditions often lead to the performance of axillary puncture or biopsy, which is associated with positive or false-negative findings[15,16]. When axillary puncture of biopsy is performed, some studies evaluate patients clinically, while others only consider the N0 axillary nodes after exclusion by ultrasound and axillary puncture. Axillary evaluation has only been important in the post-SLNB era. Few studies have exclusively evaluated axillary positivity in N0 axillary nodes since all patients were systematically subjected to AL, which justifies the present study since it is based on a historical series from the pre-SLNB era.

The present study has some limitations that must be considered. One of the major ones may actually be its merit, since this study is based on a historical series from the period before SLNB was performed, when patients underwent lymphadenectomy I-III regardless of their axillary condition. During the same period, neoadjuvant chemotherapy was beginning to be used at a greater frequency, and we attempted to exclude such patients from the sample to exclusively evaluate the axillary status in clinically N0 patients. Based on the results presented, negative axillary nodes in tumors up to 8 cm were observed in patients subjected to AL, but this finding has already been reported in tumors up to 10 cm[20]. However, the present study is grouped with a similar study[20] (Figure 2), for tumors 7.1 to 8 cm and 7.1 to 10 cm in size, 12 and 23 patients were evaluated, respectively,

and a pathological negativity rate of 25 and 11.7% was observed, respectively. The limit that should be considered acceptable for SLNB for tumors larger than 5 cm is still under debate.

Other study limitation was to not present all prognostic variable related to breast cancer, as histologic grade and the main molecular characteristics. The treatment data (Table 2) was presented to show the conditions related to low axillary recurrence in patients submitted to AL. In 2001, the molecular classification was not instituted, and some of the treatment drugs used today were quite different, a fact the reinforces the low axillary recurrence.

Since this study is based on a retrospective series, the reasons associated with the primary treatment of T4-TNM tumors are unknown, thus there may have been a selection bias. Until the publication of the 7th edition of the TNM classification system, T4-TNM tumors were considered to be associated with the presence of skin invasion, skin edema, or "peau-d'orange" appearance. In this group of patients, 32/40 presented tumors smaller than 5 cm, which indicates the presence of edema or localized infiltration as a possible criterion that can be used in these patients. The assessment of SLNB in T4 tumors is limited, and generally those studies contained a small number of patients[21-24], which prompts us to reflect on which patients would be the best candidates for SLNB.

The main benefits of SLNB include a better pathological evaluation of axillary involvement and a significant decrease in morbidity compared with AL[25-27], which justifies studies that aim at expanding SLNB indications. In recent years, the condition of clinically N0 axillary nodes has been further discussed due to the reported observer-dependent variation and to the general sensitivity of the physical examination ranges from 32 to 68% for the determination of axillary involvement[28,29]. Ultrasound has been added to the preoperative evaluation, but the result is influenced by biopsy indication criteria, and initially negative results may be modified by small unobserved tumor foci[15,30-32]
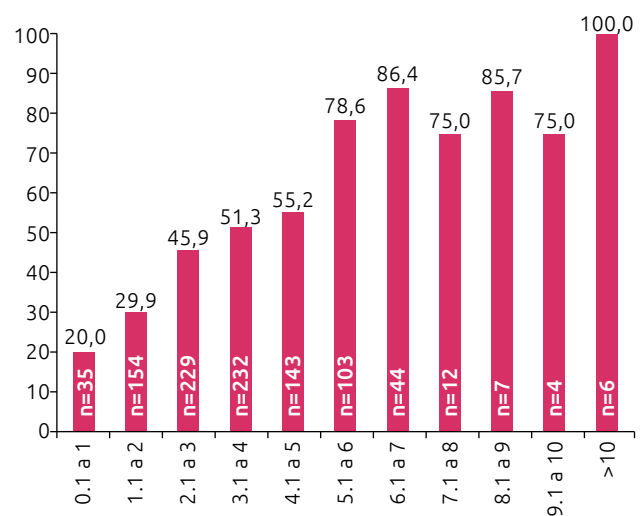

Figure 2. Percentage of metastatic disease using the current study and Corros et al. study[20].

NAC has been widely used as a way to reduce breast tumor size and to reduce axillary condition[18], but limited studies have evaluated SLNB in T3 or T4 tumors prior to NAC, and those that have been published generally involved a limited number of patients[19,23,33]. The potential advantage of SLNB before NAC is related to a higher sensitivity and a decrease in false-negative rates[19]. The identification of the axillary status prior to NAC allows more reliable clinical staging and, in the selected cases, allows for the primary surgical treatment of the breast and axillary nodes. The identification of the axillary status also makes a non-posterior axillary approach feasible[22] and safe in patients who are responsive to NAC.

Relative to the previously used treatment, breast cancer treatment has changed considerably, as taxanes have been added to anthracyclines, trastuzumab is used and hormone therapy is used for 5 or 10 years. These treatments may have a positive influence as they aim to reduce recurrence and increase survival in this group of patients. Even in these conditions, we attempted to evaluate locoregional recurrence and observed that the rate was low (8.1%) considering the tumors' size and the long follow-up time. The axillary recurrence rate was extremely low (0.4%), which is consistent with what have been reported in the literature. Veronesi et al., in a retrospective analysis of 3,548 patients with negative sentinel lymph nodes who were not subjected to AL, demonstrated that only 0.9% of the patients presented axillary recurrence and that the overall 5-year survival for the entire series was 98% after an average follow-up of 48 months[34]. In 2010, this same author reported a series of only two cases of axillary recurrence after SLNB, and those patients had a breast cancer event-free survival of approximately 89% after 10 years of follow-up[35]. These data are in agreement with the results of the NSABP B-32 trial, which presented a regional recurrence rate of 0.4% in the AL arm and 0.7% in the SLNB arm, with a false-negative rate in the AL arm of 9.8%. Even so, the disease-free survival was indistinguishable between the two groups and was approximately 82% after eight years[3].

The current consensus allows SLNB to be performed for tumors up to 5 cm, but the acceptable limit remains open. A prospective controlled study in which SLNB in one arm is compared with AL in another does not seem acceptable for us today, considering the availability of neoadjuvant and adjuvant treatment. In this sense, the present study allows us to observe that, in the presence of clinically negative axillary tumors up to 8 cm, regardless of whether the tumor is classified as T3 or T4, we can discuss the possibility of SLNB. This is because in up to 25% of these patients, AL is unnecessary and may result in negative effects in the patients.

CONCLUSION

When patients with clinically negative axillary nodes and tumors larger than 5 cm (T3-TNM), and T4-TNM were evaluated, 36.4% and 42.5%, respectively, did not present metastatic disease after AL.

Thus, SLNB can be considered in selected cases of tumors with N0 axillary nodes and in tumors larger than 5 cm and smaller than 8 cm and T4-TNM, whereas SLNB is unacceptable for tumors larger than 8.1cm. Further prospective studies are needed to evaluate the rate of axillary recurrence after SLNB since the rate is low in patients undergoing axillary lymphadenectomy.

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EVALUATION OF BONE METASTASIS OF BREAST CANCER TO LONG OR SHORT BONES, ACCORDING TO MOLECULAR SUBTYPES: RETROSPECTIVE STUDY

Avaliação da metástase óssea do câncer de mama em ossos longos ou curtos, segundo os subtipos moleculares: estudo retrospectivo

Paulo Roberto de Andrade Figaro Caldeira[1]* ⬤, Carlos Augusto Real Martinez[1] ⬤, José Roberto Fígaro Caldeira[2] ⬤

ABSTRACT

Bone is the most frequent site for breast cancer metastasis. Identifying the possible preference of bone metastasis, such as long or short bones, according to molecular subtypes, could alter oncologists approach, paying special attention to these particular group of patients reducing the side effects of the bone metastatic process, involving multidisciplinary team with orthopedists, minimizing possible sequelae of this metastatic process. Detecting different metastatic sites to long or short bones, according to the molecular subtypes and their possible correlation. Fifty-eight patients with only bone metastasis were chosen. The study material was obtained from paraffin embedded primary tumors. Statistical analysis of the data was carried out. The luminal A, luminal B, hybrid luminal, HER2 + and triple-negative / basal-like molecular subtypes were identified. The molecular subtypes compared to the age of bone implants, the distribution of bone implants, and the disease free interval were not statistically significant.

KEYWORDS: Molecular biology; breast cancer; neoplasm metastasis.

RESUMO

Acometimento ósseo é o sítio mais comum de metástase do carcinoma de mama. A identificação de possível preferência conforme os subtipos moleculares, na precocidade ou no acometimento de ossos longos ou chatos, poderia alterar a prática médica de oncologistas, dirigindo especial atenção a esses grupos de pacientes e suas possíveis complicações, em atendimento multidisciplinar com ortopedistas, minimizando possíveis sequelas desse processo metastático. Detectar a instalação dos diferentes sítios metastáticos para ossos longos ou chatos (curtos), conforme os subtipos moleculares e sua possível correlação. Foram selecionados 58 casos de pacientes com câncer de mama que apresentaram exclusivamente metástases ósseas. O material de estudo foi obtido dos tumores primários emblocados em parafina. Realizaram-se análises estatísticas dos dados. Foram identificados os subtipos moleculares luminal A, luminal B, luminal híbrido, HER2+ e triplo-negativo/basal like. Os subtipos moleculares comparados com a idade de implantes ósseos, a distribuição de implantes ósseos e o intervalo livre de doença não mostraram significância estatística.

PALAVRAS-CHAVE: Biologia molecular; neoplasias da mama; metástase neoplásica.

INTRODUCTION

Bones represent the most common site of distant metastasis of breast carcinoma. Bones from different parts of the skeleton, especially short (flat) bones, are often compromised by metastatic dissemination in women with breast cancer. It is not well understood why the initial mechanism of metastatic implants has a greater preference for bones. Among the short (flat) bones, the sequence of impairment for sternum, ribs, vertebrae and pelvis is observed. Short (flat) bones are affected before long ones[1].

Bone metastasis is strongly associated with positive estrogen receptor/negative progesterone receptor in tumors. Significant difference in tumors with estrogen receptor expression, between high and low grade with bone metastasis, suggests that different panels of molecular markers could be used to predict bone metastasis in these two groups of tumors[2].

The average time to diagnosis of only breast cancer metastasis from the last follow-up or death was 55.2 months. Only bone metastasis have been reported to occur in 17-37% of patients with distant metastasis. Metastasis to the confined distance to the skeleton presents a more favorable prognosis than other types of distant metastasis or multiple metastasis to bones and viscera. Other investigators reported that the median survival of patients with bone metastasis alone was 24-54 months. The favorable feature of the primary tumor accounts for the modest prognosis of women with only bone metastasis[3].

There is great evidence on the differences in dissemination among the biological subtypes of breast cancer. A study performed to analyze the metastatic pattern according to the biological subtype explores the corresponding prognosis. Biological subtype was defined by immunohistochemistry according to the criterion of St. Gallen, 2013, Swiss city where annual meetings of oncologists occur, in which consensus of prognoses and treatments are constructed, as adapted in Table 1. Association between biological subtypes and the distant and different locations were analyzed. Result

was reported by taking luminal A from breast carcinoma as a reference. Triple-negative breast cancer demonstrated large tropism for lung, while the non-luminal subtype human epidermal growth factor type 2 (HER2) was associated with high rate of liver metastasis. All subtypes were associated with low risk of bone only location. Briefly, this study added information to understand the complexity of breast cancer and its clinical manifestations. It also proposes categorization between different subgroups based on the immunohistochemical resources, as it could predict the preferential anatomical site of the first distant metastasis, as well as specific prognosis. It is therefore tempting to hypothesize some practical implication in terms of "adapted" management, i.e., surveillance protocols and/or therapeutic strategies that need to be verified by clinical trials[4].

Differences in the biological characteristics of breast cancer can be explained by differences in the pattern of changes between genes that act on carcinogenesis. Several studies have been conducted to determine the value of genetic changes as prognostic markers for these patients. The molecular prognostic markers used in clinical practice are: estrogen receptor (ER), progesterone receptor (PR) and tyrosine kinase receptor (ERBB2 / HER2). The presence or absence of these proteins is commonly detected using immunohistochemistry analysis. Thus, three main molecular classes were established: positive hormone receptor tumors, HER2 positive tumors and negative tumors for all the markers used. These classes have been integrated into diagnosis and treatment and help to stratify the risk of recurrence, especially in lymph node negative patients[5].

Involvement of axillary lymph nodes is considered the most informative prognostic factor. In practice, patients with four or more positive lymph nodes are considered a subgroup of unfavorable prognosis[6]. In the year 2000, Perou et al. published a work that became a reference to classify breast cancers in molecular subtypes, according to the gene expression pattern: luminal A, luminal B, superexpressor HER2, basaloid and normal-like[7].

According to Barros and Leite, these tumor subgroups present varying patterns of behavior regarding the expression of genes, the rate of tumor growth, as well as prognosis and sensitivity to treatment. According to these authors, the luminal subtype A corresponds to 30-40% of the cases; luminal B, 20 to 30%; and HER2 and basaloid, from 15 to 20% of the sample[8].

Table 1. Immunophenotypic profile to approximate molecular classification in breast carcinoma.

Molecular subtype	Profile of biomarkers
Luminal A	RE+ and/or RP+; HER2-; Ki-67<14%
Luminal B	RE+ and/or RP+; HER2-; Ki-67≥14%
Luminal hybrid	RE+ and/or RP+; HER2+
HER2+	RE-; RP-; HER2+
Triple negative	RE-; RP-; HER2-
Basal like	RE-; RP-; HER2-; CK 5/6+ and/or EGFG+

Source: Hammond et al.[10]; Cheang et al.[11]; Wolff et al.[12]; Wludarski and Bacchi[13]; Cheang et al.[14]; Bhargava et al.[15].
ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor type 2; Ki-67: protein encoded by the MKI67 gene; EGFG: epidermal growth factor gene.

OBJECTIVE

To detect the installation of different metastatic sites for long or flat (short) bones in breast cancer, according to the molecular subtypes and their possible correlation.

METHOD

This study is a historical cohort, in which 58 cases of invasive breast carcinoma, exclusively affected by bone metastasis, attended by the Department of Mastology of *Hospital Amaral Carvalho*, Jaú, São Paulo, were retrospectively selected between January 2000 and January 2012. The present study was approved by the Research Ethics Committee of the *Hospital Amaral Carvalho* and the *Plataforma Brasil*, under No. 1.546.684, dated May 16th, 2016.

Patients with breast cancer exclusively presenting bone metastasis from breast carcinoma; who underwent immunohistochemistry and adjuvant chemotherapy, according to the protocol of the Clinical Oncology Department of *Hospital Amaral Carvalho*; with adjuvant radiotherapy treatment, if indicated; with hormone therapy with tamoxifen or aromatase inhibitor, if necessary, according to the hormonal (positive) receptor status, were accepted for the present study.

Patients with distant metastasis reaching bones, viscera (lung and liver), central nervous system and skin (synchronic metastasis to different sites) were excluded from the present study.

Identification of metastatic sites

Metastatic sites were identified by imaging bone scintigraphy, radiography, computed tomography and nuclear magnetic resonance, when indicated.

Regarding the metastatic sites in the bones, these were subdivided into three groups: long bones, short (flat) bones and both.

The long bones considered were: femur, tibia, fibula, humerus, radius, ulna and clavicle. And among short or flat bones: bones of the skull, spine, sternum, ribs and pelvis.

The routine immunohistochemical analysis was done with the collaboration of Dr. Francisco Carlos Quevedo and Dr. Francisco Alves Moraes Neto, Department of Pathology, *Hospital Amaral Carvalho*, Jaú.

To facilitate the analysis of this work, and in view of tumor biological behavior, the molecular subtypes were grouped into four groups in Table 2.

RESULTS

The results are described in the form of tables and graphics. The statistical results are indicated with their corresponding p-value; and the tests are named when necessary.

Table 2. Groups of molecular subtypes.

Grouping	Subtypes
Subtype 1	Luminals A and B
Subtype 2	Group HER2+
Subtype 3	Hybrid luminal group
Subtype 4	Triple-negative and basal-like group

HER2: human epidermal growth factor type 2.

The histological classification of the tumors evaluated in this study is organized in Table 3.

About molecular subtypes and the detection of implants in long bones, short (flat) bones or both

As shown in Table 4, of the total of 58 cases, the tendency to be implanted in flat bones in the luminal molecular subtypes was evidenced, totaling 24 cases. In long bones, three cases were obtained, and in both types (long and flat), eight cases, totaling 35 cases.

DISCUSSION

The investigation of exclusively bone metastasis becomes difficult, since the metastasis are usually implanted simultaneously, in multiple sites[4].

The breast tumor samples from these 58 patients were classified according to type and histological degree.

Of this total, 51 cases were classified as ductal carcinomas, whose histological grade ranged from 1 to 3, being 1 well differentiated and 3 undifferentiated. The majority found was histological grade 2, that is, moderately differentiated. The other forms found were mucinous carcinoma (one case), lobular infiltrating (four cases) and apocrine carcinoma (one case), and one case without histological classification.

Table 3. Histological types and respective classification of histological grade.

Histological types	Number of cases
Infiltrating ductal carcinoma G3	15
Infiltrating ductal carcinoma G2	35
Infiltrating ductal carcinoma G1	1
Mucinous carcinoma	1
Infiltrating lobular carcinoma	4
Apocrine carcinoma	1
No classification for histological rating	1
Total cases	58

Table 4. Distribution of bone metastasis according to molecular subtypes.

Bones/Molecular subtypes	Long	Flat (short)	Both	Total
Luminal A	1	16	3	20
Luminal B	2	8	5	15
Hybrid	1	5	-	6
Triple-negative	1	5	5	11
HER2	-	4	2	6

HER2: human epidermal growth factor type 2.

These numbers are in agreement with the literature data, since ductal carcinomas represent 80% of the breast tumors, and the lobular tumors, approximately 10%. The other forms represent 1% of breast cancers, in their respective classifications[9].

In this sample of 58 cases, the immunohistochemical analysis revealed 35 cases classified as luminal molecular subtypes A and B; 6 cases, HER2+ subtype; 6 cases, hybrid luminal subtype; and 11 cases, triple-negative/basal like. These numbers were corroborated by Barros and Leite in a recent review article[8].

The analysis of the correlation between the molecular subtypes of breast carcinomas (luminal A and B, luminal hybrid, triple-negative/basal like, HER2+) and implants for flat bones, long bones or both (Table 4) observed 58 metastatic cases, 24 cases for flat bones in luminal molecular subtypes; 3 cases in long bones and 8 cases in long and flat bones, totaling 35 cases.

It is known that 60 to 70% of mammary tumors are of the luminal molecular subtype A and B[8]. In the sample, we identified 35 cases of luminal bone implants, a prevalence of 60.34%, considered high in comparison to other molecular subtypes. These data are corroborated by the finding in the literature, according to Wei et al.[2].

It should be noted that 24 of the 35 metastatic luminal cases were only for flat bones, that is, approximately 70% of the cases.

These findings, in general, can contribute to the clinical practice of oncologists, especially mastologists, in light of the fact that luminal subtypes have a preference for bone implants, with 60% corresponding to flat bones.

Thus, clinical practice is recommended for care in the first months of follow-up after surgery, especially in cases of luminal subtypes, for the request of bone scintigraphy in the search for possible bone metastasis.

New studies, especially using a larger sample, are necessary to affirm or not some relation of what was studied here.

CONCLUSIONS

Due to the heterogeneity of its clinical and histopathological presentation and the difficulty of selecting cases of metastatic breast cancer exclusively for bone, the present study met the proposed objectives and was able to conclude:

- Bone metastasis were found in long bones, flat bones or both, depending on the molecular subtypes of breast carcinoma and their possible correlations. Of the 58 cases analyzed, 38 were implanted in flat bones, thus distributed: 24 in the luminal subtypes, 5 in the hybrid, 5 in the triple negative and 4 in the HER2. As to the implant in long bones, 5 cases were identified, thus distributed: 3 in the luminal subtypes, 1 in the hybrid and 1 in the triple-negative/basal like. Regarding the occurrence of both types of bones, 15 metastatic implants were found: 8 in luminal subtypes, 5 in triple-negative/basal-like and 2 in HER2;

- The molecular subtypes of breast tumors classified as luminal (A and B), triple-negative/basal-like, HER2 group and hybrid luminal were identified by immunohistochemical reaction. It has also been observed that luminal molecular subtypes form the majority of bone metastasis.

Finally, these data also indicate the need for molecular-level research using these common molecular subtypes of breast cancer in the search for possible tumor markers for bone metastasis.

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BREAST CANCER SURVIVAL IN A BRAZILIAN CANCER CENTER: A COHORT STUDY OF 5,095 PATIENTS

Sobrevida do câncer de mama em um centro de câncer brasileiro: um estudo de coorte de 5.095 pacientes

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ABSTRACT

Objectives: To describe the age group, clinical stage at diagnosis, treatment, and survival rates of breast cancer patients treated in a Brazilian specialized Cancer Center. Method: A hospital-based retrospective cohort study is presented herein, on women with breast cancer diagnosed between January 1, 2000 and December 31, 2012. Data were extracted from the Hospital Cancer Registry of the A.C.Camargo Cancer Center. Data on age group, histology of the tumor, TNM classification, clinical stage and treatments were described in absolute and relative frequencies for three periods. Survival curves were estimated with the Kaplan-Meier estimator. Hazard ratio (HR) and 95% confidence interval (95%CI) were calculated for all variables. Results: A total of 5,095 female breast cancer patients were identified, with most stages classified as I and II (60%). The overall survival was 82.7% for the period of 2000–2004, and 89.9% for 2010–2012 (p<0.001). Patients with invasive ductal carcinoma, who were treated with surgery and hormonal therapy, showed a reduction in the risk of death in the most recent period HR$_{adj}$=0.42 (95%CI 0.34–0.53) (2010–2012). Conclusions: Early stage diagnosis and combined treatment (including HT) are predictive prognostic factors for high survival rates in patients with invasive breast cancer. Specialized cancer centers can provide valuable indications regarding cancer control policies, evaluating overall survival for breast cancer and its associated prognosis.

KEYWORDS: breast cancer; survival; cancer staging; cancer hospital; Brazil; South America.

RESUMO

Objetivos: Descrever as faixas etárias, estadiamento clínico ao diagnóstico, tratamento e sobrevida global das pacientes com câncer de mama tratadas em um centro de câncer brasileiro. Método: Estudo de uma coorte retrospectiva de base hospitalar, com mulheres diagnosticadas de câncer de mama entre 1º de janeiro de 2000 e 31 de dezembro de 2012. Os dados foram extraídos do Registro Hospitalar de Câncer do A. C. Camargo Cancer Center. Faixa etária, tipo histológico, classificação TNM, estadiamento clínico e tratamento foram descritos em frequência absoluta e relativa estratificados em três períodos. As curvas de sobrevida global foram estimadas pelo método de Kaplan-Meier. A Hazard ratio (HR) com intervalo de confiança de 95% foram calculados para todas as variáveis. Resultados: O total de 5.095 pacientes mulheres com câncer de mama foi identificado, a maioria era estágio inicial 60% (I e II). A sobrevida global foi de 82,7% para o período de 2000–2004 e 89,9% para 2010–2012 (p<0,001). Pacientes com carcinoma ductal invasivo que foram tratadas com cirurgia e hormonioterapia, mostraram redução do risco de morte no período mais recente HRaj=0,42 (0,34–0,53 em 2010–2012). Conclusões: Diagnóstico precoce e tratamento combinado (incluindo hormonioterapia) são fatores prognósticos preditivos para altas taxas de sobrevida em pacientes com câncer de mama invasivo. Centros especializados em câncer podem prover informações valiosas sobre as políticas de controle do câncer, avaliando a sobrevida global do câncer de mama e fatores associados ao prognóstico.

PALAVRAS-CHAVE: câncer de mama; sobrevida; estadiamento de neoplasias; institutos de câncer; Brasil; América do Sul.

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INTRODUCTION

Breast cancer is the most common cancer diagnosed in women. It is estimated that 1.67 million new cases were diagnosed worldwide in 2012. The highest breast cancer incidence rates were reported in North America, Australia, New Zealand, Europe, and Japan. Conversely, the lowest rates for breast cancer were found in Africa, Eastern Asia, and Latin America. In 2012, 52,000 deaths were attributed to breast cancer, making it the fifth most frequent cancer-related cause of death worldwide[1]. In Latin America, the incidence of breast cancer ranges from 25 to 78 per 100,000 women[2], and the highest Latin American mortality rates were observed in Argentina between 2000 and 2012[3].

In Brazil, breast cancer is the most common type of cancer in women and it is estimated that there will be 59,700 new cases in 2018, with an associated mortality rate of 14%[4]. Breast cancer mortality rates have remained stable in Brazil between 2000 and 2015[5,6], and the highest incidence rates are located in São Paulo (Southeast Brazil)[2].

Screening mammography and adjuvant therapy (treatment) contributed almost equally to the reduction in breast cancer mortality[7]. A recent study by Plevritis et al.[8] predicted that breast cancer mortality in the USA trends for women in the age group of 30–79 years, and revealed that advances in treatment, compared with screening advances, were associated with more pronounced reductions in overall breast cancer mortality between 2000 and 2012. Moreover, early staging (ES) and multidisciplinary treatment have been identified as predictive factors for better survival in invasive breast cancer patients[9-13].

Breast cancer survival has continued to increase in most countries worldwide. When considering population-based survival rates in North America and Oceania, in the period of 2010–2014, the 5-year survival rate was approximately 90%, whereas in Brazil it was 75% for the same time period[14]. However, Brazilian results were based on seven regional population-based cancer registries, and therefore the results for breast cancer survival in Brazil could have underestimated the actual survival rates.

Hospital Cancer Registries (HCR) are administrative databases at specialized cancer centers that evaluate sociodemographics, clinical staging at diagnosis, and overall and cancer-specific survival. A study conducted by the Oncocenter Foundation (FOSP), a foundation that aggregates all HCR data from the state of Sao Paulo (Southeast Brazil), analyzed the survival probabilities of 27,023 breast cancer cases from 2000 to 2005. Approximately 15.6% patients were stage IIb with 82% 5-year survival; 27% were stage III with 60% 5-year survival, and 8.5% patients were IV (metastatic disease) with 30% 5-year survival. The results reported by FOSP[15] and Tiezzi[16] reinforce that early stage at diagnosis is a strong predictor of screening actions, for the improvement of survival rates and verification of the cancer control policies' effects on the population.

The A. C. Camargo Cancer Center is a specialized cancer center with 65 years of experience in cancer care. There are few studies evaluating survival rates and clinical staging in patients with invasive breast cancer, who were treated in specialized cancer centers in Brazil or South America. Survival studies published with cancer center data could provide valuable information regarding early stage at diagnosis, treatments and survival probability of patients with invasive breast cancer. Moreover, these studies could evaluate cancer control policies based on the profile of the patients treated at these specialized cancer centers.

The objective of this study was to describe the age group, stage at diagnosis, prognostic factors, treatments performed, and overall survival of patients with breast cancer treated at the A.C.Camargo Cancer Center throughout a 13-year period (2000–2012).

METHOD

A retrospective cohort study is presented herein, encompassing women with breast cancer admitted from January 1, 2000 to December 31, 2012. The cases were extracted from the HCR at the A. C. Camargo Cancer Center.

Breast cancer characteristics were analyzed according to diagnosis data and classified into three periods: 2000–2004, 2005–2009, and 2010–2012. The variables analyzed were age group (<50 years, 50–59 years, 60–69 years, and ≥70 years), histology (ICD-O-3), Tumor, Node, Metastasis (TNM) classification, and clinical staging. Treatments were grouped into surgery, chemotherapy, radiotherapy or any treatment combination without hormonal therapy (all NoHT); surgery/chemotherapy/radiotherapy with hormonal therapy (all with HT); and only surgery and hormonal therapy (SUR+HT).

Ethical approval

This study complies with Brazil law, has received ethical approval by the Fundação Antonio Prudente — A. C. Camargo Cancer Center, reference number 2462/17. For this type of study, formal consent is not required.

Statistical analyses

Data on age group, TNM characteristics, clinical staging and treatments were described in absolute and relative frequencies for the three periods studied herein. The 5-year and 10-year overall survival rates included cases of invasive ductal carcinoma that were diagnosed between January 1, 2000 and December 31, 2012. These survival rates were calculated considering the dates of diagnosis and death or latest patient information contained in medical records. For 10-year overall survival rates, all ductal invasive cases were included between 2000 and 2006, with all patients monitored until December 31, 2017.

Five-year survival analyses were applied to the following variables: age group, tumor size (T), number of lymph nodes (N), metastasis (M), clinical stage (CS), and treatment groups. Ten-year survival analysis was carried out to verify interaction between clinical stages and treatment.

Survival curves were estimated with the Kaplan-Meier estimator, also known as the product limit estimator. The log-rank test was applied to compare the survival curves regarding each variable as well as the curves for the periods 2000–2004, 2005–2009, 2000–2004 and 2010–2012. The Cox semiparametric proportional hazards model was used to describe the differences between ductal and lobular invasive carcinoma according to age, TNM, clinical stage, treatment and period. Hazard ratio (HR) and 95% confidence interval (95%CI) were calculated for all variables. The assumption of proportional hazards was based on the Schoenfeld residuals. The significance level of the tests was fixed at 0.05. All statistical analyses were carried out with the Statistical Package for Social Science (SPSS) version 23 (IBM Corp., Armonk, NY, USA) and R software version 3.5 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of all, 5,095 females with breast cancer were treated the A. C. Camargo Center between 2000 and 2012. Most of the patients were over the age of 50 (60%; n=3,056). The most common histology was invasive ductal carcinoma (67%). The frequency of T1 cases was 31.6% for 2000–2004 *versus* 39.4% for 2010–2012. Regarding staging, 64–70% of cases were N0, with approximately 5% of cases presenting metastatic disease at diagnosis. Non-Invasive breast cancer (CS0) ranged between 15 and 18%; stage I/II accounted for 60% of the cases treated in the period. The most frequent treatment was "all with HT" (56%) (Table 1).

Five-year overall survival rates increased significantly in the three time periods regarding age, TNM classification, clinical stage and treatment. Higher rates were obtained for the most recent period, 2010–2012. The survival rate associated with tumor size ranged from 89.7% (2000–2004) to 95% (2010–2012), for T1/T2 tumors. The most pronounced increase in survival rates was associated with T3/T4 tumors, with a survival probability of 59.5% for 2000–2004 and 76.2% for 2010–2012. Regarding regional disease (N2/N3), a significant increase in survival probability (from 56.4 to 76.0%) was observed in 2010–2012. Clinical stage III and IV patients also presented increased survival, from 69% for 2000–2004 to 86.2% for 2010–2012, and from 20.7% (2000–2004) to 40.8% (2010–2012), respectively. Combined treatments (SUR, RXT, CHR) with HT were applied to most patients, increasing 5-year survival in all periods, from 88.1% (2000–2004) to 93.6% (2010–2012) (Table 2).

Ten-year overall survival increased for all time periods but it was higher in the 2010–2012 one (Figure 1A). Patients with

combined treatment associated with hormonal therapy presented higher 10-year overall survival rates, independently of their clinical stage (Figures 1B and 1C).

When analyzing the prognostic factors for all invasive breast cancer cases, the adjusted model showed an increase for risk regarding age, clinical stage and histological type. A reduction in risk was observed for treatment type and period of diagnosis (supplementary Table 1). Based on these initial overall results, the prognostic factors were stratified by histological group into ductal and lobular invasive. Increased risk was obtained for both histological groups for age and clinical stage, and a reduction in risk was obtained for the combined treatment with hormonal therapy (all with HT and SUR+HT) (Table 3).

DISCUSSION

At the A.C.Camargo Cancer Center, in the 2000–2012 period, 5-year survival rates for ductal carcinoma breast cancer were approximately 90%, 60% of patients were post-menopausal women (>50 years old), 40% of patients were classified as T1 and 64.3% as N0. Clinical stage I/II accounted for 60.8% of the cases identified in the 2010–2012 period. Throughout the 13-year study period, the 5-year overall survival rates increased for all three time periods studied herein, from 82.7 to 89.9%. The independent prognostic factors were treatment combination including hormonal therapy, clinical stage, age, histology and period.

The profile of this cancer center reflects early diagnoses with efficient treatment in an older population. This means that the policies adopted by the Brazilian government could have influenced to improve early staging at diagnosis and better treatment outcome, hence improving survival rates. Approximately 75% of health coverage in Brazil is public (the remainder is associated with private health plans), and breast cancer has been recognized as a health priority[17]. Data related to early diagnosis in the publicly-funded Brazilian healthcare system highlighted striking regional inequalities in access to early detection and surgery, with the lowest access rates in the North Region and the highest in the South Region[18]. In the study herein presented, the cancer center treated public and private patients indistinctively, and it was not possible to classify patients regarding type of coverage.

Aging is one of the main risk factors for breast cancer. The demographic changes experienced by Latin America were expected to cause epidemiological shifts and increase breast cancer incidence[10]. At the A. C. Camargo Cancer Center, 60% of patients were older than 50 at the time of diagnosis. This is the age profile for breast cancer incidence in Latin America[1], where older women are biologically having more favorable tumors[19] and therefore better survival prognosis. In a study conducted in the South of Brazil, Schneider and d'Orsi[20] reported that older patients presented higher survival rates then young women.

Table 1. Characteristics of 5,095 female breast cancer patients treated at the A. C. Camargo Cancer Center between 2000 and 2012.

Variables	Diagnosis Period			
	2000–2004 (n=1,499) N (%)	2005–2009 (n=1,853) N (%)	2010–2012 (n=1,743) N (%)	Total (n=5,095) N
Age group (years)				
<50	624 (41.6)	750 (40.5)	665 (38.2)	2,039 (40.0)
50–59	365 (24.3)	504 (27.2)	513 (29.4)	1,382 (27.1)
60–69	273 (18.2)	331 (17.8)	339 (19.4)	943 (18.5)
≥70	237 (15.8)	268 (14.5)	226 (13.0)	731 (14.3)
Histology				
In situ (non-invasive)	229 (15.3)	338 (18.2)	283 (16.2)	850 (16.7)
Invasive ductal	1,078 (71.9)	1,207 (65.1)	1,147 (65.8)	3,432 (67.4)
Invasive lobular	77 (5.1)	160 (8.6)	175 (10.0)	412 (8.1)
Other histological types	115 (7.7)	148 (8.0)	138 (7.9)	401 (7.9)
Tumor size (T)				
Is	229 (15.3)	338 (18.2)	283 (16.2)	850 (16.7)
1	473 (31.6)	672 (36.3)	687 (39.4)	1,832 (36.0)
2	446 (29.8)	507 (27.4)	453 (26.0)	1,406 (27.6)
3	59 (3.9)	71 (3.8)	114 (6.5)	244 (4.8)
4	224 (14.9)	210 (11.3)	166 (9.5)	600 (11.8)
No data available	68 (4.5)	55 (3.0)	40 (2.3)	163 (3.2)
No. lymph nodes (N)				
0	966 (64.4)	1,300 (70.2)	1,120 (64.3)	3,386 (66.5)
1	302 (20.2)	304 (16.4)	417 (23.9)	1,023 (20.1)
2	158 (10.6)	147 (7.9)	111 (6.4)	416 (8.2)
3	14 (0.9)	46 (2.5)	57 (3.3)	117 (2.3)
No data available	59 (3.9)	56 (3.0)	38 (2.2)	153 (3.0)
Metastasis (M)				
0	1,424 (95.0)	1,761 (95.0)	1,641 (94.1)	4,826 (94.7)
1	75 (5.0)	92 (5.0)	102 (5.9)	269 (5.3)
Clinical Stage				
0	229 (15.3)	338 (18.2)	283 (16.2)	850 (16.7)
I	412 (27.5)	569 (30.7)	548 (31.4)	1,529 (30.0)
II	472 (31.5)	556 (30.0)	513 (29.4)	1,541 (30.2)
III	262 (17.5)	262 (14.1)	285 (16.4)	809 (15.9)
IV	75 (5.0)	92 (5.0)	102 (5.9)	269 (5.3)
No data available	49 (3.2)	36 (1.9)	12 (0.7)	97 (1.9)
Treatment				
All No HT	470 (31.4)	553 (30.3)	543 (31.3)	1,566 (30.8)
All with HT	857 (57.2)	1,013 (55.4)	966 (55.7)	2,836 (56.1)
SUR+HT	172 (11.5)	262 (14.3)	224 (12.9)	658 (13.1)

HT: hormonal therapy; SUR: surgery.
Source: Hospital Cancer Registry, 2017.

However, Guerra et al.[21] did not find differences in survival rates regarding different age groups in Southeastern Brazil (Juiz de Fora, Minas Gerais).

Ductal invasive carcinoma was responsible for 72–67% of the cases identified; other Brazilian studies have reported that ductal invasive carcinoma rates were 81.7% in Curitiba[22] and 63.9% in Santa Maria[23]. Invasive lobular carcinoma was observed in 14% of the patients over the age of 70, which is higher than the observed in Curitiba (4%)[22].

Herein, 60.8% of cases were diagnosed at early clinical stages (CS I/II), similarly to Florianopolis (64.3%)[20] and Santa Maria (77.4%)[23], and higher than those reported for other cancer institutions

in Curitiba (47.4%)[22] and Rio de Janeiro (48.3%)[13]. This difference could be related to the profile of these institutions, as those in Curitiba and Rio de Janeiro treat more patients from the public healthcare system. Regarding clinical staging in Minas Gerais (1998–2000), 74% of early diagnosis were associated with private patients, while this percentage was 63% for public patients[6].

The frequency of clinical stage III/ IV was 19–22% for the time period studied herein (2000–2012), which was lower than the reports of other Brazilian cancer centers (30–44%)[13,20,21]. The A. C. Camargo Cancer Center has diagnosed a high proportion of women with early stage breast cancer, and this profile can be a result of government policies directed to mammography

Table 2. Five-year overall survival (OS) for patients with invasive breast ductal carcinoma at the A. C. Camargo Cancer Center between 2000 and 2012 (n=3,432) according to age, tumor size (T), number of lymph nodes (N), metastasis (M), clinical stage, and treatment by period.

Variables	2000–2004		2005–2009		2010–2012	
	Cases (Events)	5-year OS¶	Cases (Events)	5-year OS¶	Cases (Events)	5-year OS¶
General	1,078 (187)	82.7	1,207 (181)	84.9	1,147 (108)	89.9
Age group (years)						
<50	445 (65)	85.4	505 (62)	87.6	460 (38)	91.3
50–59	263 (36)	86.3	329 (36)	89.0	335 (28)	91.1
60–69	206 (45)	78.2	219 (32)	85.3	201 (18)	90.1
>70	164 (41)	75.0	154 (51)	65.8	151 (24)	82.2
T						
T1/T2	783 (81)	89.7	949 (82)	91.3	896 (42)	95.0
T3/T4	242 (98)	59.5	224 (84)	62.3	224 (50)	76.2
N						
N0	605 (59)	90.2	768 (61)	92.0	646 (25)	95.8
N1	278 (56)	79.9	253 (44)	82.3	339 (37)	88.2
N2/N3	149 (65)	56.4	152 (60)	60.2	137 (31)	76.0
M						
M0	1,020 (141)	86.2	1,138 (135)	88.0	1,069 (64)	93.5
M1	58 (46)	20.7	69 (46)	33.3	78 (44)	40.8
Clinical Stage						
I	335 (13)	96.1	456 (19)	95.8	420 (5)	98.7
II	416 (55)	86.8	446 (50)	88.7	415 (26)	93.3
III	229 (71)	69.0	215 (60)	71.8	225 (29)	86.2
IV	58 (46)	20.7	69 (46)	33.3	78 (44)	40.8
Treatment						
All NoHT	328 (93)	71.6	333 (91)	72.3	351 (61)	80.2
All with HT	670 (80)	88.1	742 (70)	90.5	697 (43)	93.6
SUR + HT	75 (12)	84.0	117 (9)	92.2	93 (1)	98.9

HT: hormonal therapy; SUR: surgery; p<0.05.

screening[8]. However, it is limited and has heterogeneous coverage throughout Brazil[16,24].

At the A. C. Camargo Cancer Center, the 5-year overall survival rates for breast invasive ductal carcinoma stage I were 96.1% for the 2000–2004 period, increasing to 98.7% for 2010–2012. The highest increase in survival rates occurred for stage IV breast cancer, which doubled from 20.7 to 40.8% in the period of 2010–2012. Such improvement in the most recent period could be due to changes in therapeutic procedures, such as the inclusion of new, targeted therapies[8]. The Brazilian Study Group on Breast Cancer (better known by its acronym in Portuguese, GBECAM) reported that women treated in public institutions presented more advanced staging at diagnosis, difficulties in accessing modern therapies, and worse overall survival than patients treated at private institutions[25]. Factors such as delays in diagnosis, due to low levels of awareness regarding cancer, slow implementation of mammography screening, limited quality of surgery treatment and restricted access to radiotherapy and modern systemic therapies could be responsible for disparities in the survival rates for breast cancer[26].

Treatment with HT was the best prognosis indicator for breast cancer survival and early clinical stage at the A. C. Camargo
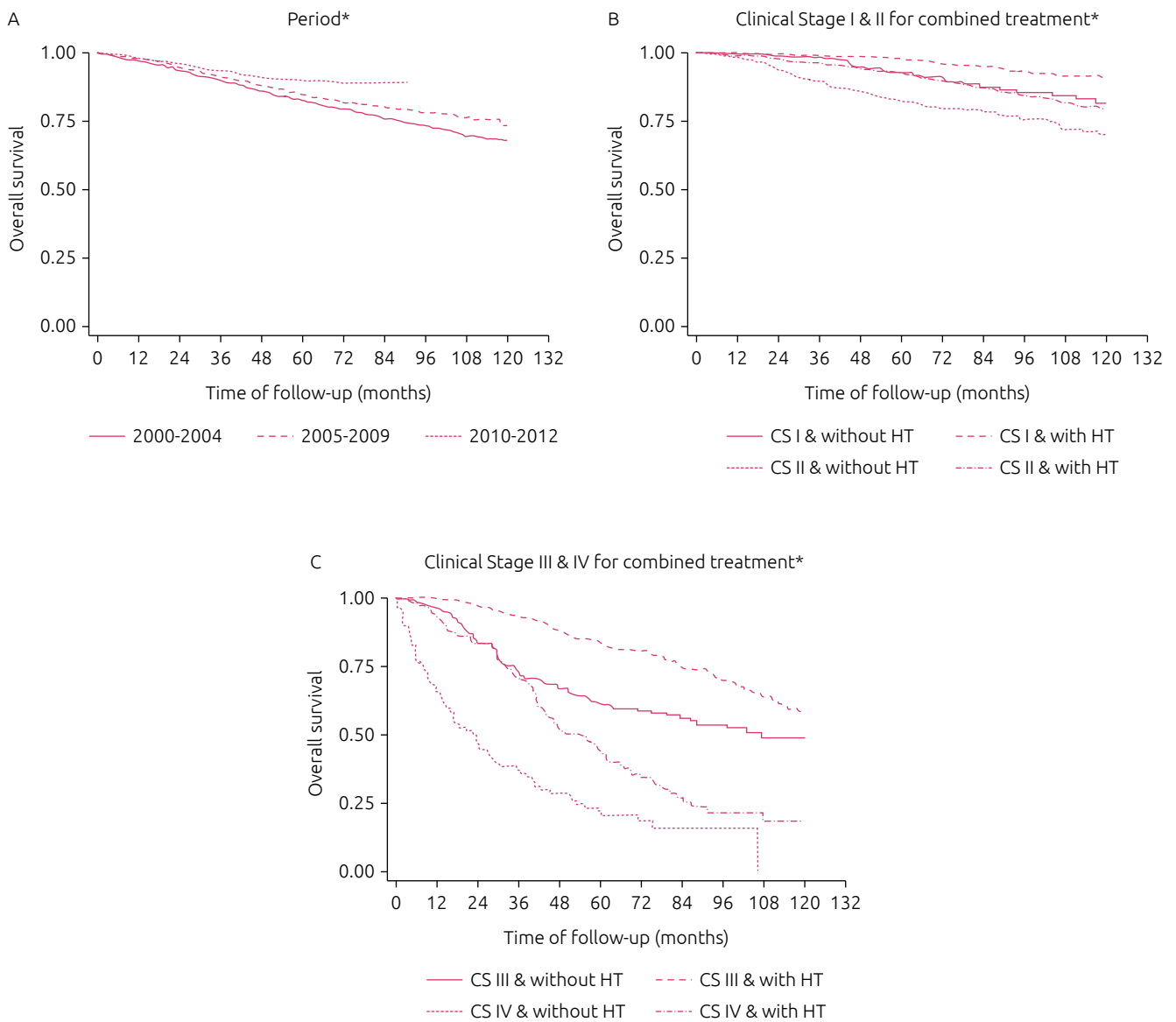
*p<0.001

Figure 1. Overall 10-year survival rates for patients with invasive breast ductal adenocarcinoma by period (A) and treatment versus clinical stage (B, C) at the A. C. Camargo Cancer Center, 2000–2012.

Cancer Center. In developed countries, widespread population screening and treatment improvements are factors that have influenced reductions in breast cancer mortality[27]. In Brazil, screening for breast cancer has been recommended but has not been fully organized or implemented throughout the country[28]. However, breast cancer mortality rates have remained stable across all Brazilian regions[5,6].

Data regarding hormonal receptors (*e.g.*, estrogen and progesterone), human epidermal growth factor receptor 2 (HER2) and other factors such as histological grade were not analyzed in this work and could limit its conclusions.

An important aspect of this study is the encompassment of a cohort of more than 5,000 women, who were treated for breast cancer at a single institution. In addition, prognostic factors, such as 10- and 5-year overall survival data, were examined throughout a 13-year period, with follow-up losses under 6.5%. This study contributes with a further comprehension of the epidemiological profile of breast cancer cases treated within specialized cancer centers. Herein, it was observed that the A. C. Camargo Cancer Center presented better overall survival rates for older women and for advanced stages of invasive breast cancer over 13-year period. Nevertheless, the combination of treatment including

Table 3. Prognostic factors associated with invasive breast cancer according to histological type data from the Hospital Cancer Registry, 2017, of the A. C. Camargo Cancer Center, 2000–2012.

Characteristics	Ductal		Lobular	
	HR unadjusted	HR adjusted	HR unadjusted	HR adjusted
Age group (years)				
<50	1	1	1	1
50–59	0.90 (0.73–1.11)	1.10 (0.89–1.36)	2.12 (1.17–3.85)*	2.03 (1.09–3.79)*
60–69	1.35 (1.10–1.67)*	1.49 (1.20–1.86)**	1.46 (0.73–2.90)	1.65 (0.80–3.42)
≥70	2.71 (2.23–3.29)**	2.66 (2.16–3.26)**	3.41 (1.86–6.23)**	3.65 (1.91–6.98)**
Tumor size (T)				
T1	1		1	
T2	2.68 (2.14–3.36)**		1.39 (0.78–2.50)	
T3	3.72 (2.64–5.22)**		2.94 (1.46–5.92)*	
T4	9.13 (7.31–11.40)**		5.90 (3.33–10.47)**	
Lymph node (N)				
N0	1		1	
N+	2.97 (2.53–3.48)**		2.65 (1.70–4.16)**	
Clinical Stage				
I	1	1	1	1
II	2.56 (1.98–3.30)**	2.40 (1.86–3.10)**	1.20 (0.62–2.32)	1.22 (0.63–2.39)
III	5.87 (4.56–7.56)**	5.71 (4.41–7.39)**	4.38 (2.39–8.02)**	4.04 (2.17–7.53)**
IV	24.47 (18.70–32.00)**	24.72 (18.76–32.58)**	15.40 (8.11–29.23)**	15.93 (7.98–31.80)**
Treatment				
All No HT	1	1	1	1
All with HT	0.44 (0.38–0.52)**	0.44 (0.37–0.51)**	0.39 (0.24–0.62)**	0.48 (0.29–0.80)*
SUR + HT	0.42 (0.30–0.58)**	0.60 (0.42–0.85)*	0.17 (0.07–0.42)**	0.32 (0.13–0.80)*
Period				
2000–2004	1	1	1	1
2005–2009	0.79 (0.67–0.94)*	0.81 (0.68–0.96)*	0.94 (0.57–1.55)	1.16 (0.67–1.98)
2010–2012	0.50 (0.40–0.62)**	0.42 (0.34–0.53)**	0.70 (0.38–1.31)	0.57 (0.29–1.13)

HR: hazard ratio; HT: hormonal therapy; SUR: surgery; *p<0.05; **p<0.001.

hormonal therapy was the best predictive prognostic factor for survival in patients with invasive ductal breast cancer.

AUTHORS' CONTRIBUTION

Makdissi FB reviewed manuscript. Leite FPM wrote the manuscript. Peres SV analyzed the data, interpreted the results and wrote the manuscript. Silva DRM interpreted the results and wrote the manuscript. Oliveira MM reviewed the manuscript. Lopez RVM analyzed and discussed the data. Sanches SM reviewed the manuscript. Gondim GR reviewed the manuscript. Iyeyasu H discussed and reviewed the manuscript. Calsavara VF analyzed data and interpreted the results. Curado MP designed and supervised the research, interpreted and discussed the data. All authors approved the final version of the manuscript to be published.

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Supplementary Table 1. Prognostic factors associated with invasive breast cancer survival Hospital Cancer Registry (HCR), A. C. Camargo Cancer Center, 2000–2012.

Characteristics	HR unadjusted	HR adjusted
Age group (years)		
<50	1	1
50–59	0.99 (0.82–1.21)	1.18 (0.97–1.44)
60–69	1.36 (1.11–1.66)*	1.50 (1.22–1.85)**
≥70	2.77 (2.30–3.32)**	2.74 (2.26–3.33)**
Tumor size (T)		
T1	1	
T2	2.47 (2.00–3.04)**	
T3	3.66 (2.70–4.97)**	
T4	8.55 (6.96–10.50)**	
Lymph node (N)		
N0	1	
N+	2.93 (2.52–3.40)**	
Clinical stage		
I	1	1
II	2.33 (1.84–2.95)**	2.21 (1.74–2.80)**
III	5.59 (4.43–7.05)**	5.47 (4.32–6.94)**
IV	22.95 (17.92–29.38)**	23.39 (18.13–30.17)**
Histology		
Ductal	1	1
Lobular	1.19 (0.95–1.49)	1.36 (1.08–1.71)*
Treatment		
All No HT	1	1
All with HT	0.45 (0.39–0.52)**	0.44 (0.38–0.51)**
SUR + HT	0.38 (0.28–0.52)**	0.54 (0.39–0.75)**
Period		
2000–2004	1	1
2005–2009	0.81 (0.69–0.95)*	0.82 (0.70–0.97)*
2010–2012	0.52 (0.43–0.64)**	0.43 (0.35–0.54)**

HR: hazard ratio; HT: hormonal therapy; SUR: surgery; *p<0.05; **p<0.001.

USE OF COMPRESSION GARMENT IN THE TREATMENT OF MALIGNANT LYMPHEDEMA IN A PATIENT WITH RECURRENT BREAST CANCER: CASE REPORT

Utilização de vestimenta compressiva no tratamento do linfedema maligno em paciente com câncer de mama recidivado: relato de caso

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ABSTRACT

Introduction: Malignant lymphedema is a rapidly progressive condition, and its treatment is a major challenge. **Objective:** To demonstrate the benefit of using compression garments in reducing limb volume and improving the symptoms of a patient with malignant lymphedema with recurrent breast cancer. **Case report:** A 67-year-old woman, diagnosed with a 2.3 cm, triple negative, invasive ductal carcinoma in the left breast, submitted to quadrantectomy with axillary dissection (T2aN1bM0). The patient developed benign lymphedema after eight years of surgery, but only started complex decongestive physiotherapy three years after the diagnosis, presenting an important improvement. The following year, the patient returned with complaints of worsening lymphedema. At the examination, there was an expressive volume increase and areas of vascular alteration in the left upper limb (LUL) and in the anterior quadrant of the thorax. The exams confirmed axillary vein thrombosis due to tumor obstruction. Lymphoscintigraphy showed unsatisfactory lymphatic drainage. As a last treatment option, the use of LUL low elastic compression garment was adopted, after poor success after the use of multi-layered compression bandages. LUL volume was 6,158.1 mL prior to using the garment. After ten days of continuous use, the volume decreased to 5,174.2 mL. In the last evaluation, the volume was 4,510.8 mL, presenting a reduction of 1,647.3 mL (26.7%). The patient developed acute respiratory failure caused by pleural metastasis, and died. **Conclusion:** The compression garment provided benefits such as significant improvement in the feeling of heaviness in the limb due to the reduction of volume and in the ease of putting on and taking off the garment in or make the hygiene, when compared to the multilayer compression bandages. Other advantages were the reduction of costs and the promotion of well-being.

KEYWORDS: lymphedema; breast cancer; physiotherapy specialty.

RESUMO

Introdução: O linfedema maligno é uma condição com rápida progressão, e seu tratamento é um grande desafio. **Objetivo:** Demonstrar o benefício do uso de vestimenta compressiva na redução do volume do membro e na melhora dos sintomas de uma paciente com linfedema maligno após câncer de mama recidivado. **Relato de caso:** Colocar paciente de 67 anos, sexo feminino, com diagnóstico de carcinoma ductal invasor em mama esquerda com 2,3 cm e triplo negativo, submetida a quadrantectomia com esvaziamento axilar (T2aN1bM0). A paciente desenvolveu linfedema benigno após oito anos de cirurgia, porém só iniciou tratamento fisioterapêutico com terapia física complexa descongestiva três anos após o diagnóstico, apresentando melhora importante. No ano seguinte, retornou ao consultório com queixa de piora do linfedema. Ao exame, apresentava aumento de volume expressivo e áreas de alteração vascular no membro superior esquerdo (MSE) e no quadrante anterior do tórax. Os exames confirmaram trombose de veia axilar por obstrução tumoral. A linfocintilografia demonstrou ausência de drenagem linfática satisfatória. Adotou-se, como última opção de tratamento, o uso da vestimenta compressiva de baixa elasticidade de MSE, após

baixa resposta do enfaixamento compressivo multicamadas. O volume do MSE era de 6.158,1 mL antes do uso da vestimenta. Após dez dias contínuos de uso, o volume diminuiu para 5.174,2 mL. Na última avaliação, o volume era de 4.510,8 mL, apresentando redução de 1.647,3 mL (26,7%). A paciente evoluiu com insuficiência respiratória aguda ocasionada por metástase pleural à direita, vindo a falecer. **Conclusão:** A vestimenta proporcionou benefícios como melhora importante da sensação de peso no membro devido à redução de volume e facilidade em colocar e retirar a vestimenta para fazer a higiene, quando comparada ao enfaixamento compressivo multicamadas. Outras vantagens foram a redução de custos e a promoção do bem-estar.

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

INTRODUCTION

Lymphedema is a chronic progressive disease that occurs frequently after cancer treatment with lymph node dissection due to breast cancer resulting from the accumulation of fluid in the interstitial tissues. According to meta-analysis, the incidence in cancer survivors is 15%[1]. The incidence of lymphedema in patients with breast cancer submitted to axillary dissection is 17% at 2 years and 30% at 5 years postoperatively[2].

Malignant lymphedema occurs when there is lymphatic flow impairment in the lymphatic channels and / or lymph nodes due to the spread of the malignant tumor, which can be acutely onset with rapid progression, resulting in changes in skin color and muscle weakness, which may be the first tumor recurrence signal[3].

Complex decongestive physiotherapy (CDPT,) is divided into two phases: the intensive phase, which must occur daily or on alternate days and the maintenance phase, which the patient commences when the limb volume does not present further reduction, appropriate elastic compression (compression arm sleeve) must be used and skin care and exercises should be maintained[4].

CDPT is recognized as a treatment for malignant lymphedema and consists of inelastic compression bandaging, exercises and skin care, and may or may not use manual lymphatic drainage (MLD)[5,6].

CDPT helps to reduce limb volume and lymphedema severity, it also aids the improvement of range of motion, pain and weight. However, patients with malignant lymphedemas need prolonged follow-up time, which requires more physiotherapy and consequently additional costs[5].

Few studies have examined the treatment of malignant lymphedema. A systematic review on the management of cancer-related lymphedema in palliative care showed the subject to be a major challenge for health professionals. Most of the studies were case reports, and there was no randomized clinical trial. One retrospective study on MLD; two case studies on compression therapy; and three case studies on CDPT were identified[7]. However, none of them used garments as part of the treatment.

The objective of this case report was to demonstrate the benefit of using compression garments in reducing limb volume and consequently improving the symptoms of a patient with malignant lymphedema after recurrent breast cancer.

CASE REPORT

Female, 67 years old, with diagnosis of a 2.3 cm, triple negative invasive ductal carcinoma of the left breast. She was submitted to quadrantectomy with left axillary dissection on November 1st, 2003. Fifteen lymph nodes were removed, of which six had lymph node metastasis, classified as stage T2aN1bM0. The patient underwent six sessions of chemotherapy (December 2003 to May 2004) and radiotherapy in breast and supraclavicular fossa (June to August 2004).

During a consultation with the doctor in 2006, the patient reported feeling of heaviness and volume increase in the left upper limb (LUL), however in the following appointments she did not have any further complains. In 2011, the patient suffered a fall on her LUL and, after this episode, noticed the appearance of benign lymphedema. She started treatment with CDPT for lymphedema on August 28th, 2014 through MLD, limb hydration, compression bandaging, and exercises. The patient was also given orientation regarding skin care and self-massage. Because she lived in a city that did not offer this treatment, she had to travel to our institution.

In the manual perimetry applied to the truncated cone formula, the volume of the right upper limb (RUL) was 2,760 mL and 5,108 mL in the LUL, i.e., there was a difference of 2,348 mL (85.1%) between the limbs. The diagnosis of lymphedema is made when the difference is greater than 10%. Lymphedema was classified as severe according to the Stillwell classification[8,9] (normal: 0-10%, mild: 10-20%, moderate: 20-40%, marked 40-80%, and severe: over 80%).

After six weeks of treatment, LUL volume reduced to 4,274.3 mL, a reduction of 833.7 mL (16.3%). The patient also presented improvement of fibrosis upon palpation. The difference in volume between the limbs was 1,514.3 mL, which corresponds to 54.9%. The patient was discharged from the intensive phase of the CDPT on October 9th, 2014, and continued to the maintenance phase because there was no further reduction in limb volume.

Two monthly evaluations were performed, in which limb volume maintenance was verified through the use of a compression arm sleeve associated with exercises and self-drainage. On January 5th, 2015, however, the patient returned complaining of worsening lymphedema, significant felling of heaviness and pain. Upon examination, the patient had increased volume and areas of neovascularization in the LUL and in the anterior quadrant

of the thorax (Figure 1). The difference in volume between the limbs was 2,012.3 mL (72.9%).

The patient was referred to the doctor for suspicion of axillary vein thrombosis, which was confirmed with echocardiography. It was suspected that the thrombosis was caused by tumor obstruction, a hypothesis also confirmed by biopsy. Malignant lymphedema was diagnosed in the LUL and quadrants (breast and back).

The patient returned to the physiotherapy and began to undergo chemotherapy in April 2015. It was expected that the limb volume would be reduced by tumor reduction, but even with the chemotherapy and the physiotherapy (hydration, multilayer compression bandaging using short extensibility bandages, application of kinesio tape in axillary and axillo-inguinal lymphatic anastomoses and exercises), there was no significant improvement. The patient had difficulty attending the physiotherapy appointments twice a week and could not do the compression bandaging because she lived alone.

Lymphoscintigraphy (Figure 2) demonstrated that there was no satisfactory Lymphatic drainage in LUL, and no marking of lymph node drainage even after imaging performed six-hours after. No dermal reflux was observed. Therefore, upon receiving the result of the lymphoscintigraphy, the MLD treatment was stopped as it did not present benefits, and only the use of compression bandages was used in order to reduce limb volume associated with exercise and skin care.

After several attempts to decrease limb volume in order to improve functionality, aesthetic and joint pain of the shoulder due to the weight, the use of an inelastic LUL garment associated with home exercises was adopted as the last option. This decision was made because the patient was missing many appointments and the limb volume was increasing.

Neoprene low elastic compression garment (Figure 3) was proposed as an alternative to reduce visits to physiotherapy, since the patient lived in another city and was too weak to travel due to the chemotherapy treatment. The garment allowed the patient to readjust the pressure in the limb several times a day.

The LUL volume was 6,158.1 mL before using the compression garment and the RUL volume was 2,760 mL, a difference of 3,408.1 mL (123.9%). The garment was tailor-made and adjusted for the patient on November 16th, 2015. After 10 days of use, the volume decreased to 5,174.2 mL, a difference of 983.9 mL. In the evaluation on December 21th, 2015, the volume had further reduced: 4,609.3 mL, with a difference of 2,424.2 mL (88.1%) between the limbs. The last evaluation occurred on February 4th, 2016 with a volume of 4,510.8 mL, i.e., a reduction of 1,647.3 mL (26.7%) since the beginning of the use of the compression garment. The difference between limbs was 1,760.8 mL (64.0%) (Figure 4).
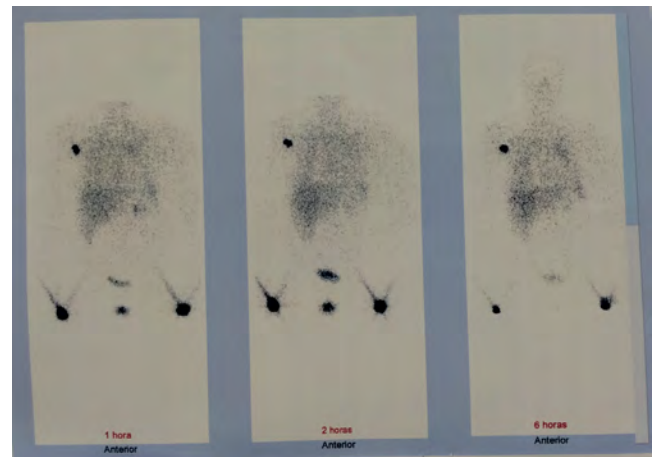
Figure 2. Lymphoscintigraphy of a patient with lymphedema related to breast cancer. The exam shows absence of marking of drainage lymph nodes even in the image delay of six hours and absence of dermal reflux.

Figure 1. Neovascularization with indefinite limits in limb and quadrants in a patient with breast cancer with tumor recurrence.

Figure 3. Garment for treatment of lymphedema of upper limb. The first picture shows the first day of use; the second photo, ten days of use; and the third photo, six weeks of use. The garment had to be adjusted twice by new seams in the interval between the photos.

After the reducing the volume of the malignant lymphedema, the patient reported an improvement in the feeling of heaviness and pain in the shoulder joint, as well as in the practicality of removing the garment and during self-hygiene. In the last evaluation, a new garment was requested, since the previous one was very loose, even after being readjusted twice by a seamstress. Table 1 shows the evolution of lymphedema from benign to malignant, as well as the degree of lymphedema during the proposed treatments.

The patient underwent several thoracentesis due to consecutive pleural effusions, as she presented with right pleural metastasis. The patient was hospitalized in March 2016 for the above procedures, and did not return for reassessment due to acute respiratory failure, and passed way on April 5th, 2016.

DISCUSSION

There is a shortage of studies on the efficacy of physiotherapy for malignant lymphedema. Most research cites medical treatment for pain relief and is comprised of case reports. Early physiotherapy is indicated because malignant lymphedema tends to progress, causing discomfort, pain and psychological problems[3]. Compression bandaging treatment is one of the main tools for decreasing limb volume, but requires correct pressure applied by a specialist physiotherapist. By replacing it with a compression garment, activities such as taking a bath and performing activities of daily living become easier and thus improve the patient's daily routine.

It is common for the patient to present symptoms such as heaviness, pain and discomfort, which significantly reduce the physical function, mobility and ability to perform daily activities, with consequent worsening of quality of life. Patients with lymphedema with obstruction due to tumor recurrence tend to present more psychological and emotional concerns[10,11].

In this case reported, the feeling of heaviness was quite expressive, which improved with the use of the compression garment. Based on manual perimetry, it is known that there is a strong correlation between the feeling of heaviness and limb volume increase[12]. The feeling of heaviness is improved when the volume of the limb is reduced.

In a study with patients who had malignant lymphedema undergoing treatment with CDPT, but without MLD, Hwang et al.[6] demonstrated that quality of life was improved and upper and lower limb pain and volume was reduced, even without MLD. Therefore, MLD may not present benefits for patients with malignant lymphedema, as opposed to inelastic compression, as observed in the present study. MLD was not performed when the patient was using the compression garment since lymphoscintigraphy showed significant obstruction due to tumor recurrence.

A recent pilot study evaluated 12 individuals with malignant lymphedema, demonstrating that CDPT was effective for a cohort of patients with palliative cancer and limited survival. The authors, however, applied an individualized program using: bandaging, MLD, compression mesh, kinesio tape, exercises, deep breathing techniques, education and skin care. There was improvement in limb volume, quality of skin and quality of life related to lymphedema[13], however, for the patient in this study,

Figure 4. Lymphedema of the left upper limb after axillary lymph node dissection as treatment for breast cancer before the use of garment (A) and after six weeks of continuous use (B).

Table 1. Evolution of benign lymphedema treatment that became malignant, with respective dates, left upper limb volume, difference between the volume of the affected limb and the control in mL and in%, lymphedema grade and proposed treatment.

Evaluation date	Treatment	LUL volume (mL)	Difference between limbs (mL)	Difference between limbs (%)	Level of lymphedema[8,9]
08/28/2014	No treatment	5,108.0	2,348.0	85.1	Severe
10/09/2014	CDPT – IP	4,274.3	1,514.3	54.9	Marked
01/05/2015	CDPT– MP	4,782.0	2,012.3	72.9	Marked
11/16/2015	CDPT– IP	6,158.1	3,408.1	123.9	Severe
12/21/2015	Garment	4,609.3	2,424.2	88.1	Severe
02/04/2016	Garment	4,510.8	1,760.8	64.0	Marked

LUL: left upper limb; CDPT:complex decongestive physiotherapy ; IP: intensive phase; MP: maintenance phase.

bandaging did not present good results and volume reduction was more effective after using the garment.

The use of compression garments for the treatment of lymphedema helps to reduce limb volume, is more practical than traditional compression bandaging, and useful for patients who live far from the treatment center or who are not available for physiotherapy[14.] The compression garment was a good alternative, since the patient lived in another city, where there was no specialized physiotherapeutic treatment services. The patient could readjust the cord during the course of the day, when she noticed that the limb volume was diminishing and the garment was loose. This was an important advantage over the compression bandage, because in order to use the compression bandages, she would have had to move from her city every other day. She was able to make less trips due to compression garment and thus reducing the cost of the treatment.

The inelastic compression garment is a very useful tool in the treatment of malignant lymphedema, as it results in a reduction in the number of visits to the physiotherapist, facilitates self-care and provides more independence, well-being and cost effective[15].

CONCLUSION

The compression garment provided benefits such as reducing limb volume and consequently improve in the feeling of heaviness, shoulder pain, well-being and ease of putting on and taking off the garment in order to perform personal hygiene, and it is presented as a good treatment option for malignant lymphedema. In addition, it provides more convenience and practicality to the patient when compared to the compression bandage. Until now, there has not been any study demonstrating the use of compression garments in the treatment of malignant upper limb lymphedema. The performance of new studies, with more expressive samples and good designs is suggested in order to test the efficacy of the management of malignant lymphedema in palliative care.

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PAGET'S DISEASE IN A MALE PATIENT: CASE REPORT

Doença de Paget do mamilo em paciente masculino: relato de caso

Francine Hickmann Nyland[1]*, Patrícia Moreira Rebello da Silva[1], Mário Casales Schorr[1], José Luiz Pedrini[1]

ABSTRACT

Paget's disease is a rare entity that accounts for 1 to 3% of breast tumors. Occurrence in male patients is even less common. Literature has reported only 24 cases in the last 20 years. We described the case of a 62-year-old male patient that sought medical care due to erosion and eczema on left nipple. After skin biopsy, the clinical suspicion of Paget's disease was confirmed by histological and immunohistochemical studies, which enabled the proper surgical and oncological treatment.

KEYWORDS: Paget's disease, mammary; breast; breast neoplasms

RESUMO

A Doença de Paget do mamilo é uma entidade rara, representando 1 a 3% dos carcinomas de mama. Sua presença em pacientes masculinos é ainda menos comum, com apenas 24 casos na literatura nos últimos 20 anos. Em nosso relato de caso, descrevemos um paciente masculino de 62 anos que procurou atendimento por erosão e eczema no mamilo esquerdo. Após biópsia de pele, a histologia e o estudo imuno-histoquímico confirmaram a suspeita clínica de Doença de Paget do mamilo, possibilitando o tratamento cirúrgico-oncológico adequado.

PALAVRAS-CHAVE: Doença de paget mamária; mama; neoplasias da mama.

INTRODUCTION

Sir James Paget coined the name Paget's Disease following the report of several cases, including 15 patients, in 1874. He firstly believed the disease would be a benign condition, although it was associated with a malignant disorder. In most cases, the lesion manifests as an ulceration or erythema on the nipple with skin scaling, which also evolves with exudate or papillary cluster. Differential diagnosis should include areolar eczema, contact dermatitis, and actinic dermatitis[1]. Diagnosis still poses challenge when it comes to the male population, as men usually seek health services late and incorrect treatments are established due to differential diagnoses and occurrence rarity.

CASE REPORT

A 62-year-old male patient without comorbidities and non-smoker sought medical care in the Mastology Clinics due to one-year evolution erosive lesion on left breast. He had family history of a twin sister who died due to breast neoplasm at age 48 and a brother with skin melanoma. Physical examination showed erosion of the left nipple-areolar complex with hyperemia and skin scaling associated with retroareolar densification, without no other finding (Figure 1). Mammogram showed focal distortion on the left breast's upper side and microcalcifications (Figures 2 and 3). Ultrasound imaging showed hypoechogenic area (not nodule-shaped), with thin formation of posterior acoustic shadowing, hyperechogenic focuses on its inner side, and presence of dermis and hypodermis thickening in areolar region. The patient underwent nipple (skin) biopsy that presented "atypical cells of Paget standard." The results of immunohistochemical study were compatible with Paget's Disease (Figure 4). After diagnosis, the patient received treatment and then mastectomy and sentinel lymph node investigation were conducted. The definite anatomopathological examination also showed a 2.2-cm ductal carcinoma in situ on retro-areolar region, which was associated with invasive breast carcinoma. The sentinel lymph node tested negative for metastases. After surgical recovery, the patient received chemotherapy with cyclophosphamide and docetaxel, and then adjuvant tamoxifen. He has been on medical follow-up for a year without evidence of recurrence.
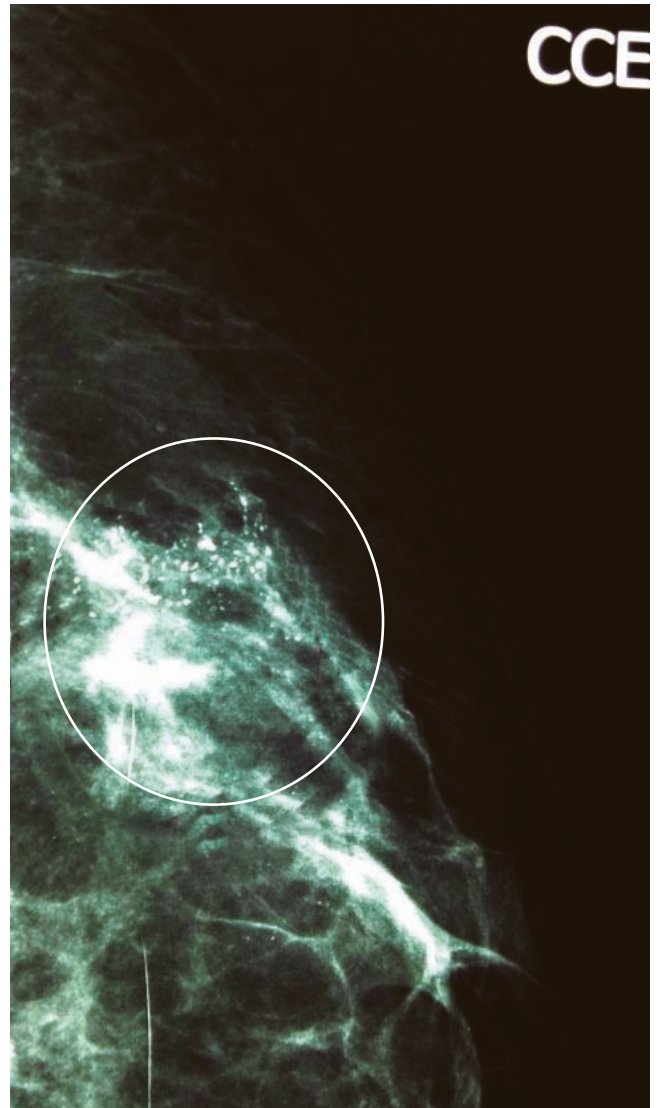

Figure 2. Mammography with evidence of architectural distortion and microcalcifications (left craniocaudal view).

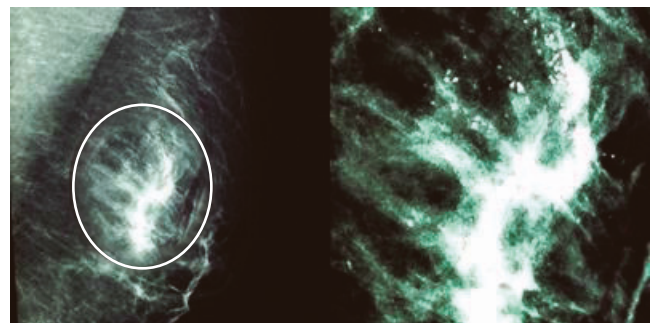**Figure 1.** Lesion with erosion in left nipple-areolar complex.

Figure 3. Mammography with evidence of architectural distortion and microcalcifications (left medial and lateral oblique views).

DISCUSSION

Paget's Disease is a rare presentation of breast cancer that accounts for 1 to 3% of all cases. Occurrence in men is even rarer (24 cases have been reported in literature since 1997)[2]. Most lesions are associated with adjacent breast malignant disease; however, it can also coexist with carcinoma in situ or in its pure form[3]. The classical risk factors for male breast neoplasm are described in patients with Paget's Disease—mutations in BRCA 1 and 2 genes (Breast Cancer 1 and 2), Klinefelter syndrome, previous exposure to radiation, endocrine alterations with tendency to hyperstrogenism, among others. Nevertheless, there is not enough evidence of their association with this specific pathology.

Clinically, most patients present with eczema or nipple ulceration which have been present for several months. Pruritus, serous exudate, crusts, and papillary cluster may also be present[1]. Differential diagnosis must be performed with conditions
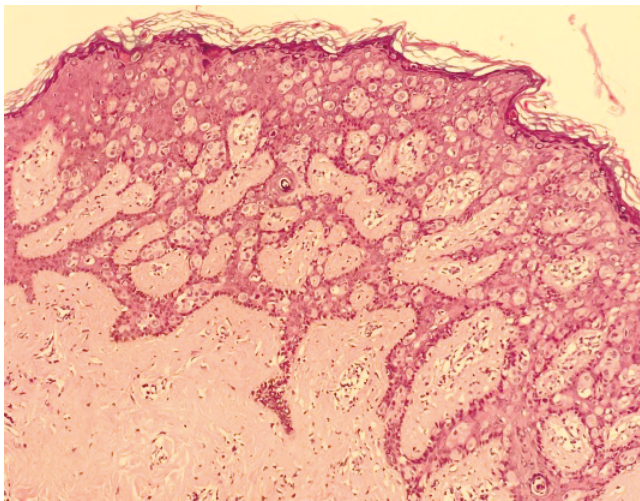

Figure 4. Histological cut of areolar tissue showing epidermis invasion by Paget's cells with abundant cytoplasm, vesicular nucleus, and prominent nucleoli.

such as nipple eczema, psoriasis, nipple adenomatosis, melanoma, contact dermatitis, and actinic dermatitis[2].

This type of neoplasm is histologically characterized by nipple epidermis infiltration with aggregates of large and ovoid tumoral cells, with abundant cytoplasm, vesicular nucleus, and prominent nucleoli (Figure 4)[4].

Imaging findings are not specific. The mammographic examination has only 34% sensitivity, but it is useful to evaluate disease extension in the event of findings[5]. Ultrasound imaging is also used, especially when the mammography is negative for tumors.

Kim et al. (2010) found that magnetic resonance imaging (MRI) with contrast revealed morphological alterations in 87.5% of the lesions diagnosed as Paget's disease compared to 20.0% by mammogram and 60.0% by ultrasound. In addition, MRI shows the lesion in mammary parenchyma in 100% of cases[6]. Thus, breast MRI has been more used, with studies of small series that demonstrate advantages, especially when it comes to spotting an occult disease[1].

Paget's disease prognosis in men is quite worse compared to the female population and depends mainly on the adjacent malignant disease. Mastectomy is the most used treatment for men—with axillary emptiness or sentinel lymph node investigation—, with adjuvants according to the general principles of breast neoplasm treatment.

CONCLUSION

Reports related to Paget's Disease of the breast in males are rare in the literature. Many considerations and recommendations for the diagnosis and treatment of this pathology are obtained from studies conducted with females. Therefore, the difference of prognosis for women and men is still the target of questioning. Hence, it is greatly important to suspect and recommend biopsy in alterations of men's nipple aiming at providing patients with an early treatment.

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