MASTOLOGY

Sociedade Brasileira de
Mastologia

21º CONGRESSO BRASILEIRO DE MASTOLOGIA

11 a 14 de Julho de 2018

Centro de Convenções da Amazônia - Hangar
Belém - Pará - Brasil

CONVIDADOS INTERNACIONAIS:

Dra. Kelly Hunt - EUA
Cirurgia conservadora após "dowstage"
tumoral: seguro ou arriscado?

DR. CHRISTOPHE HO QUOC - Lyon - França
Lipoenxertia para sequelas
de cirurgias conservadoras.

TEMAS PRINCIPAIS:

IMAGEM MAMÁRIA

ONCOGENÉTICA

TERAPIA NEOADJUVANTE

CIRURGIA AXILAR

COMPLICAÇÕES CIRÚRGICAS

ALTO RISCO

O FIM DA CIRURGIA?

Acesse nosso site:
www.mastologia2018.com.br
e faça sua inscrição

Realização:

Sociedade Brasileira de Mastologia

Sociedade Brasileira de Mastologia
Regional Pará

Coordenação e Organização:

name
comunicação integrada

CONTENTS

ONCOPLASTIC TRAINING IN THE UK AND PERSPECTIVES FOR THE FUTURE

Treinamento em oncoplastia no Reino Unido e perspectivas para o futuro

Richard Rainsbury[1]*

INTRODUCTION

The delivery of breast services in the UK has undergone fundamental changes over the last 30 years, driving up standards of practice and improving outcomes across the board. At the same time, the quality and variety of surgical techniques available has changed beyond all recognition, with the emergence of a wide range of new oncoplastic (OP) techniques that are now freely available to all National Health Service (NHS) patients. The development and implementation of an innovative model of cross-speciality training in the UK was one of the most important factors underlying this remarkable achievement. Quite by chance, a number of unanticipated events converged almost simultaneously, each one playing a vital role in guiding and accelerating changes in training and service delivery. A closer look at these events will help to provide some insight into the UK experience.

INCREASING SPECIALISATION

The introduction of the UK NHS Breast Screening Programme in 1988 was the catalyst that triggered off a range of inter-related developments. These included the formation of a new Breast Group within the British Association of Surgical Oncology. This nascent professional body represented the increasing number of specialist breast surgeons, and was responsible for the development of a raft of clinical practice guidelines, backed up by a framework of quality assurance and accreditation to underpin the emergence of a new generation of specialist breast units. Inevitably, this development led to much greater specialisation in breast surgery, with the gradual loss of the traditional skills of the general surgeon. These were slowly replaced by new skills in OP and reconstructive surgery, reflecting and driving the growing popularity of these techniques. OP guidelines were published for the first time, describing the options available in OP surgery and expected outcomes, establishing a new set of standards[1].

CHANGING EXPECTATIONS

The following decade saw a big rise in demand for access to OP services, as a result of much greater patient, public and professional interest in these techniques. For the first time, national guidelines relating to the management of early breast cancer stated that patients facing mastectomy had the right to be offered immediate breast reconstruction and OP repair of resection defects[2]. This was a real turning point in the evolution of OP surgery in the UK, but the number of skilled breast and plastic surgeons was insufficient to meet a rising demand. Only a handful of breast surgeons had acquired these skills, and of the 300 consultant plastic surgeons with responsibility for a population of almost 60,000,000 people, nearly all were expected to cover a wide range of other more general plastic procedures.

A LOOMING CRISIS FOR BREAST SURGERY

By the late 1990's, breast surgery was facing a real crisis. Few trainees in general surgery were choosing to sub-specialise as breast surgeons, and a national survey confirmed that the lack of technical challenges, low levels of operative satisfaction and high levels of clinical stress were the root causes for its low popularity[3]. General surgical trainees no longer had the opportunity to acquire the much wider range of skills enjoyed by their predecessors, as a result of foreshortened training programmes and the European Working Time Directive, both of which limited opportunities to gain experience. Those trainees selecting breast surgery highlighted the need to develop more advanced breast-specific skills, including breast reconstruction, a skill prioritised by 80% of respondents.

The National Breast Group addressed this looming crisis by coordinating three key developments, signalling the birth of OP surgery in the UK:

[1]Royal Hampshire County Hospital – Winchester, England, United Kingdom.
***Corresponding author:** rrainsbury@aol.com
Conflict of interests: nothing to declare.

- A new national portfolio of comprehensive cadaver-based courses for teaching key steps in OP and reconstructive surgery in a laboratory setting. This was an outstandingly successful development, which remains very popular nowadays;
- A new sub-speciality Breast Curriculum was developed by the Breast Group and endorsed by two statutory bodies in the UK: the Joint Committee for Specialist Training in General Surgery and the General Medical Council. For the first time, breast surgeons in training were expected to acquire a wide range of competencies in OP and reconstructive techniques. This was the first curriculum in Europe to include OP skills as an integral part of a breast surgeon's training;
- Informal cross-speciality training arrangements that existed between breast and plastic surgeons were formalised when an Oncoplastic Training Interface Group (TIG) was established in 2000. The group included representatives of both parent Associations and this seminal event marked the birth of the Oncoplastic Breast Surgeon, trained in all aspects of diagnosis, resection, reconstruction and oncological management. The agreed aims of the TIG were to
  - Improve service to patients by facilitating interface training;
  - Develop cross-speciality training for registrars and consultants;
  - Provide training for more junior surgeons.

SUSTAINING AND SUPPORTING OP TRAINING

The falling popularity of breast surgery coincided with a rising demand for specialist breast surgeons at a time when women were increasingly becoming more aware of their right to be offered breast reconstruction. As a result, breast surgery was designated a 'shortage speciality' by the Department of Health, which was looking for innovative solutions to improve recruitment. The TIG grasped this opportunity, submitting a proposal for national funding of nine new Oncoplastic Fellowships at a cost of *circa* £ 500,000 per annum. Large Regional OP centres were chosen to host the Fellowships following a competitive national selection process. Key criteria for selection included staffing by a full complement of breast and plastic surgeons working together, enabling comprehensive training in a full range of OP procedures, backed up by an active programme of audit and research. The Department of Health continues to fund this scheme today, which has trained more than 100 Fellows from a background of breast and plastic surgery over the last 15 years. These post-holders have personally performed an average of 100 major OP procedures during their Fellowship year. More than 80 have been appointed as consultant OP surgeons, and most are now involved in training the next generation.

Collaboration between breast and plastic surgeons through their Associations continues to strengthen and sustain the OP project. The successful implementation of a centrally funded National Mastectomy and Breast Reconstruction audit (NMBRA) of >5,000 reconstructions in 2008[4] was followed by the development of new OP guidelines in 2012[5]. Both were major projects that would have failed without robust cross-speciality collaboration and support. The NMBRA reported unexpectedly high rates of infection, implant loss and readmission, and generated more than 60 new indicators of good practice. This large-scale audit also disclosed significant variations in access to reconstruction across the UK, with rates varying between 10–43%[6]. These inequalities are being addressed as increasing numbers of trained OP surgeons are securing consultant appointments. The key quality standards that underpin the new OP guidelines[5] are aimed at improving access, reducing post-operative pain and avoiding the high complication rates disclosed by the NMBRA.

THE BREAST-PLASTIC PROFESSIONAL INTERFACE

The relationship between breast and plastic surgeons has been 'sinusoidal' over the last two decades, but with more peaks than troughs. Both specialities have grown to appreciate the 'win-win' outcome of cross-speciality training and working. For breast surgeons, this has resulted in the acquisition of OP skills for breast conservation and immediate reconstruction at the time of mastectomy. For plastic surgeons, the gains have included more cross-speciality referrals for free flap reconstruction and revisional surgery, as well as closer multi-disciplinary working.

Both groups have benefitted from more sophisticated training initiatives, such as the Master's Degree in OP Surgery. Developed by the University of East Anglia, this is a modular programme backed up by tutor-moderated on-line discussion and hands-on courses[7]. Above all, patients are benefitting from much more information and choice, and from more frequent cross-specialty referral when indicated or requested.

EUROPEAN DEVELOPMENTS

The provision of OP services and the training and type of surgeon providing these services varies enormously from country to country in mainland Europe. Surgeons come from widely different backgrounds including general surgery, surgical oncology, gynaecology and plastic surgery, and work both independently or in a team. The European Society of Mastology (EUSOMA) has been instrumental in establishing standards by developing a common framework of quality assurance and accreditation for organisations providing breast services. This framework has been endorsed by the European Breast Specialist Societies, and is being adopted by increasing numbers of multi-disciplinary teams.

The process began in 2000 with the publication of European guidelines that established the requirements for specialist breast units[8]. This was followed in 2007 by a second EUSOMA publication defining new standards for the training of specialised health professionals. For the first time, this established a requirement that breast surgeons should be trained in reconstruction[9]. Finally, EUSOMA produced a more detailed document in 2013 updating the requirements for specialist breast services. This document underpins a new Europe-wide process for the quality assurance and accreditation of breast centres[10]. As part of the process of accreditation, centres must provide evidence that both breast reconstruction and OP breast conservation are provided 'in-house'. Twenty-six European breast centres have been able to meet this standard to date and have received official accreditation, and this number continues to rise.

These developments have recently been recognised and supported by the European Union of Medical Specialists, which has laid down the requirements for a Specialist Certificate in Breast Surgery[11]. Regular examinations are held to assess training, knowledge, skills and experience, including OP experience. This certificate is fast becoming a 'must have' qualification, raising standards of training and OP surgery right across Europe.

CURRENT TRENDS

Changing the curriculum to include reconstruction 20 years ago continues to have a profound effect on the availability and variety of OP techniques currently used in the UK. Today's curriculum for general surgeons[12] still requires trainees with an interest in breast surgery to be 'emergency safe'. This limits the time available for them to acquire more complex skills in reconstruction, including pedicle and free-flap autologous techniques. As a result, the skill base of a new consultant today is mainly limited to implant-based techniques and increasingly the use of OP breast-conserving surgery, including volume replacement and volume displacement.

For patients, implant reconstruction is an attractive option, with a short hospital stay, less risk, less disability and a quicker recovery, when compared with more complex flap-based techniques. For surgeons, implant reconstruction is less technically demanding, the procedures are quicker, and the avoidance of major flap-based complications greatly simplifies post-operative care. For hospitals, performing implant reconstruction brings financial and logistic benefits, with faster theatre procedures, a higher throughput of cases and a shorter post-operative stay, compared with more complex techniques. The recent introduction of the acellular dermal matrix (ADM) for lower pole implant cover remains a key factor accelerating the use of implant-based reconstruction. The use of implants accounted for 55% of all reconstructions in the UK in 2014[13] and 80% of all reconstructions in the US by 2016[14]. The higher rates recorded in the US may reflect the more generous reimbursement allowed for implant compared with flap-based techniques[15].

These trends give cause for concern. Although the longer-term outcomes of ADM/implant techniques are largely unknown, the superior clinical and patient-reported outcomes following autologous compared with implant reconstruction have been clearly demonstrated up to 20 years following the original procedure[16-18]. In the long run, the 'quick fix' offered by implant reconstruction and favoured by many patients, surgeons and healthcare providers may prove to be a 'ticking time bomb'. Year-on-year, unplanned revisions for implant loss, reconstruction failure or poor cosmetic outcome have been shown to escalate almost exponentially[19].

FUTURE CHALLENGES

The substantial rise in the popularity of OP surgery is creating new challenges for clinicians, service providers, and patients alike.

A need for better outcome data

The increase in the number and variety of techniques reported in the literature is taking place without good quality outcome data to inform treatment decisions. Much of the data quoted is based on Level 2/3 evidence from cohort studies or systematic reviews, or Level 4/5 evidence from small retrospective case series or expert opinion. One of the largest systematic reviews of OP surgery published to date included more than 42,000 cases of reconstruction, and concluded that 'at present the breast reconstruction outcome literature is inconsistent, and lacks methodological rigor... a core outcome dataset is strongly recommended'[20].

Recently, a number of new initiatives have been launched in the UK to address this problem. Progress was first made with the prospective NMBRA of more than 5,000 patients, which disclosed significantly better patient-reported outcomes following autologous reconstruction compared with implant techniques, 18 months following surgery[4]. Another national database (the Hospital Episode Statistics Database) more recently reported significantly lower revision rates following autologous *versus* implant reconstruction in nearly 14,000 patients[21]. These results have been further validated by a prospective multicentre cohort study of more than 2,000 patients undergoing immediate implant or implant/ADM reconstruction in more than 80 centres: the UK iBRA study[22]. This study has recently disclosed an unexpectedly high complication rate, with 18% of patients requiring an unplanned return to theatre by three months, and the longer-term outcomes of implant-based procedures are awaited.

These and other initiatives are beginning to inform evidence-based practice, but many more are needed to drive up standards and to help patients make informed choices. In future, full discussion and frank disclosure about risks and benefits of different

techniques should be mandatory and is likely to influence the prevailing trend towards implant-based reconstruction.

More objective decision-making tools

New tools are becoming available which have the potential to transform the identification of those patients most likely to benefit from OP breast conservation. The recent description of 'core datasets' to identify these patients (e.g. BCCT.core[23]) is leading to the development of much more sophisticated tools to predict the aesthetic outcomes of breast conservation.

An example of this is the PICTURE™ project[24] which uses software to 'fuse' individual patient's data, generated from multiple sources (patient and tumour-specific data, 3D photography, prone MRI and MR elastography) to create an 'avatar' of post-operative appearance. The patient is then able to see images of her predicted appearance following straightforward breast-conserving surgery. These will help her decide whether she wishes to undergo a more complex OP procedure to prevent the likely deformity. This novel approach will help to bring much greater objectivity to pre-operative decision-making.

Extending the OP skill-base to reduce mastectomy rates

Many of the longer-term problems associated with total mastectomy and implant reconstruction (progressive asymmetry, capsule formation, implant failure, extrusion, multiple surgical revisions, etc.) may be minimised or avoided altogether by greater use of OP conservation techniques. These are already extending the role of breast conservation in the UK, and their use has increased from 1 to 6% of all breast-conserving procedures between 2000–2014[25]. Their popularity is likely to escalate further still as the indications for breast conservation are extended to include larger, multi-centric tumours, traditionally treated by mastectomy[26].

A recent decision by the UK Specialist Advisory Committee for General Surgery will allow future general surgical trainees with a sub-speciality interest in breast surgery to spend the final two years of their training programme focusing exclusively on breast disease, including the acquisition of advanced oncological and OP skills. This seminal decision will extend the portfolio of breast surgeons, and will equip them with the skill-base necessary to perform many of these new mastectomy-avoiding procedures.

Cost-containment and new ways of working

Greater use of OP and reconstructive procedures is increasing the financial challenges of delivering increasingly sophisticated specialist care today. Costs are destined to escalate, with up to two-thirds of breast cancer patients in the US undergoing contralateral risk reducing surgery, often combined with immediate reconstruction[14]. In the US[27], Northern Europe[28] and elsewhere[29], the use of risk-reducing bilateral mastectomy and immediate

reconstruction for high genetic or familial risk is also increasing. In the UK, the overall cost for this procedure is around £ 15,000[30]. This is considerably more than the costs of other forms of risk-reduction, including endocrine manipulation and bilateral salpingo-oophorectomy. In future, decisions about funding for these major OP procedures may depend on health economics — such as the cost per Quality Adjusted Life Year (QALY), compared to other risk-reducing options.

Limitations to the maximum number of OP procedures that the UK NHS will be able to afford are currently under consideration. Funding is already restricted to a maximum of two procedures in some parts of the country. Providing high quality evidence that demonstrates the cost-effectiveness of OP surgery — based on clinical and patient reported outcomes — is an urgent challenge for current and future generations.

Finally, for closer working relationships between breast and plastic surgeons to be successful, traditional territorial boundaries need to be broken down further still. Much has been achieved, with interface fellowships[31], a joint OP Masters degree[7], joint national audits[4,22], and joint oncoplastic guidelines[5], resulting in more integrated, streamlined care. In spite of these efforts to promote integration, much remains to be done. Recent evidence suggests that breast surgeons in the UK extended their OP skill-base between 2010 and 2015, with 75% requesting further training. But the skill-base of plastic surgeons remained static during this period, with only 27% requesting further training[31]. If this trend continues, OP conservation and breast reconstruction will be carried out more and more by breast surgeons as they become increasingly skilled at the full range of procedures, with the exception of free-flap techniques requiring the microvascular skills of plastic surgeons.

CONCLUSIONS

OP surgery is now widely available in the UK as a result of a range of cross-specialty developments that have created an integrated model of care. This initiative would have failed without the early commitment of a small group of breast and plastic surgeons who were willing to work together to develop a new sub-specialty, with a patient focus. The model is now evolving asymmetrically, with breast surgeons beginning to perform most of the OP surgery, in spite of repeated attempts to create a 'generic' OP service with equal input by breast and plastic surgeons.

This situation has emerged because most breast surgeons have given up their general surgical practice and became totally committed to the concept of OP surgery and the acquisition of new skills. In contrast, plastic surgeons remain relatively scarce in the UK, and are expected to retain a range of general plastic skills to enable them to provide both elective and emergency services. This is limiting their opportunities for cross-specialty practice, even for those with OP training and skills. Their more

traditional role performing autologous breast reconstruction is however expanding, with a much greater awareness of the indications for these more complex techniques, and increasing requests to salvage failed implant reconstructions.

The UK is fortunate to enjoy a world-class OP service as a result of two decades of cross-speciality cooperation, central financial support and national training initiatives. It is hoped that our experience will provide a useful template for other countries and healthcare systems seeking to develop an integrated OP service. Continued professional commitment and bilateral support are the most important ingredients for a service to thrive and respond to future challenges.

REFERENCES

1. Association of Breast Surgery at BASO, Association of Breast Surgery at BAPRAS, Training Interface Group in Breast Surgery, Baildam A, Bishop H, Boland G, et al. Oncoplastic breast surgery- a guide to good practice. Eur J Surg Oncol. 2007;33(Suppl.1):S1-23.

2. National Institute for Health and Care Excellence. NICE Clinical Guideline 80- early and advanced breast cancer [Internet]. 2009 [cited on Oct 23, 2017]. Available from: www.nice.org.uk/cg80

3. Rainsbury R, Browne J. Specialisation in breast surgery: opinions of the UK higher surgical trainee. Ann R Coll Surg Engl. 2001;83(Suppl):S298-301.

4. National Mastectomy and Breast Reconstruction Audit [Internet]. 2011 [cited on Oct 23, 2017]. Available from: http://content.digital.nhs.uk/catalogue/PUB02731/clin-audi-supp-prog-mast-brea-reco-2011-rep1.pdf

5. Rainsbury D, Willett A. Oncoplastic breast reconstruction. Guidelines for best practice [Internet]. 2012 [cited on Oct 23, 2017]. Available from: http://associationofbreastsurgery.org.uk/media/1424/oncoplastic-breast-reconstruction-guidelines-for-best-practice.pdf

6. Jeevan R, Mennie J, Mohanna P, O'Donoghue JM, Rainsbury RM, Cromwell DA. National trends and regional variation in immediate breast reconstruction rates. Br J Surg. 2016. DOI: 10.1002/bjs.10161

7. Down S, Pereira J, Leinster S. 256541 - The specialist clinical masters qualification in oncoplastic breast surgery: A globally accessible degree supporting clinical excellence. Proceedings Annals Surg Oncol. 2017.

8. Blamey R, Cataliotti L. The requirements of a specialist breast unit. Eur J Cancer. 2000;36:2288-93.

9. Cataliotti L, De Wolf C, Holland R, Marotti L, Perry N, Redmond K, et al. Guidelines on the standards for the training of specialised health professionals dealing with breast cancer. Eur J Cancer. 2007;43:660-75.

10. Wilson A, Marotti L, Bianchi S, Biganzoli L, Claassen S, Decker T, et al. The requirements of a specialist breast centre. Eur J Cancer. 2013;49:3579-87.

11. European Union of Medical Specialists. Division of Breast Surgery of the Section of Surgery and European Board of Surgery [Internet]. 2014 [cited on Oct 23, 2017]. Available from: www.uemssurg.org/divisions/breast-surgery

12. The Intercollegiate Surgical Curriculum Programme [Internet]. 2016 [cited on Oct 23, 2017]. Available from: www.iscp.ac.uk/

13. Mennie J, Mohanna P-N, O'Donoghue J, Rainsbury R, Cromwell D. National trends in immediate and delayed post-mastectomy reconstruction procedures in England: a seven-year population-based cohort study. Eur J Surg Oncol. 2017;43:52-61.

14. American Society of Plastic Surgeons. Plastic Surgery Statistics [Internet]. 2016 [cited on Oct 23, 2017]. Available from: www.plasticsurgery.org/news/plastic-surgery-statistics

15. Albornoz C, Bach P, Mehrara BJ, Disa JJ, Pusic AL, et al. A paradigm shift in US breast reconstruction: increasing implant rates. Plast Reconstr Surg. 2013;131:15-23.

16. Clough K, O'Donoghue J, Fitoussi A, Nos C, Falcou MC. Prospective evaluation of late cosmetic results following breast reconstruction: 1. Implant reconstruction. Plast Reconstr Surg. 2001;107:1702-9.

17. Pusic A, Matros E, Fine N, Buchel E, Gordillo GM, Hamill JB, et al. Patient-reported outcomes 1 year after immediate breast reconstruction: results of the Mastectomy Reconstruction Outcomes Consortium Study. J Clin Oncol. 2017;35:2499-506.

18. Atisha D, Rushing C, Samsa G, Locklear TD, Cox CE, Shelley Hwang E, et al. A national snapshot of satisfaction with breast cancer procedures. Ann Surg Oncol. 2015;22:361-9.

19. Odofin O, Harris K, Paramanathan N, Laws S, Rainsbury R. The impact of providing an oncoplastic service on the workload of a specialist unit. Breast J. 2011;17:371-6.

20. Potter S, Brigic A, Whiting P, Cawthorn SJ, Avery KN, Donovan JL, et al. Reporting clinical outcomes of breast reconstruction: a systematic review. J Natl Cancer Inst. 2011;103:31-46.

21. Mennie J, Mohanna P-N, O'Donoghue J, Rainsbury R, Cromwell D. Rates of secondary surgery following immediate post-mastectomy reconstruction in the English NHS hospitals: a national cohort study of 13,736 women. Eur J Surg Oncol. 2017;43:S2-3.

22. Potter S, Conroy E, Williamson P, Thrush S, Whisker LJ, Skillman JM, et al. The iBRA (implant breast reconstruction) study. Protocol for a prospective multi-centre cohort study to inform the feasibility, design and conduct of a pragmatic randomised clinical trial comparing new techniques of implant-based breast reconstruction. Pilot Feasibility Studies. 2016;2:41.

23. Cardoso M, Cardoso J, Amaral N, Azevedo I, Barreau L, Bernardo M, et al. Turning subjective into objective: the BCCT.core software for evaluation of cosmetic results in breast cancer conservative treatment. Breast. 2007 Oct;16(5):456-61.

24. Picture. Patient Information Combined for the Assessment of Specific Surgical Outcomes in Breast Cancer [Internet]. [cited on Oct 23, 2017]. Available from: www.vph-picture.eu/

25. Mennie J. Personal communication. Figures based on UK Hospital Episode Statistics (HES). 2001-2014.

26. Silverstein M, Savalia N, Khan S, Ryan J. Extreme oncoplasty: breast conservation for patients who need mastectomy. Breast J 2015:21:52-9.

27. Cemal Y, Albornoz C, Disa J, McCarthy CM, Mehrara BJ, Pusic AL, et al. A paradigm shift for US breast reconstruction: Part 2. The influence of changing mastectomy patterns on reconstruction rate and methods. Plast Reconstr Surg. 2013;131:320e-6e.

28. Hagen A, Maehle L, Veda N, Vetti HH, Stormorken A, Ludvigsen T, et al. Risk-reducing mastectomy, breast reconstruction and patient satisfaction in Norwegian BRACA 1/2 mutation carriers. Breast 2014;23:38-43.

29. Semple J, Metcalf K, Lynch H, Kim-Sing C, Senter L, Pal T, et al. International rates of breast reconstruction after prophylactic mastectomy in BRCA 1 and BRCA 2 mutation carriers. Ann Surg Oncol. 2013;20:3817-22.

30. Robertson S, Summerhayes C, Laws S, Rainsbury R. Resource implications of risk-reducing mastectomy and reconstruction. Eur J Surg Oncol. 2016;42:45-50.

31. Joint Committee on Surgical Training. Reconstructive & Aesthetic Surgery [Internet]. 2017 [cited on Oct 23, 2017]. Available from: https://www.jcst.org/training-interface-groups/reconstructive-aesthetic-surgery/

32. Challoner T, Skillman J, Wallis K, Vourvachis M, Whisker L, Hardwicke J. Oncoplastic techniques: attitudes and changing practice amongst breast and plastic surgeons in Great Britain. Breast. 2017;34:58-64.

VALIDATION OF NCCN CRITERIA FOR GENETIC TESTING IN HBOC SYNDROME IN BRAZIL

Validação dos critérios da NCCN para testagem genética na Síndrome de Câncer de Mama e Ovário Hereditários no Brasil

Andre Vallejo da Silva[1]*, José Claudio Casali da Rocha[2,3], Guilherme Olivetti Guarneri[3]

ABSTRACT

Objective: To identify genetic mutations in BRCA1 and BRCA2 genes in women suspected of HBOC syndrome and to correlate them with NCCN testing criteria to verify its impact on mutation finding rates, as well as to identify the relevant criteria, the frequency and type of found mutations and the relative importance of each NCCN criteria. **Methodology:** A database with all the cases tested for HBOC by the second author from 2010 to 2016 was built, and the variables of interest were annotated and then analyzed with a statistical package to find the relevant variables. **Results:** A total of 171 patients was tested and 38 had deleterious mutations (22%). Criteria with significant association to the present mutations were the total numbers of relatives with cancer (p=0.02) and Ashkenazi lineage (p=0.001). Age of the youngest relative with cancer below 49 was not significant in this sample (p=0.1). There is a strong correlation between mutated patients and NCCN criteria (p=0.0001), but we found no such correlation between the presence of NCCN testing criteria and the presence of mutation (p=0.11). Regarding the use of NCCN criteria to find BRCA mutations, sensitivity was 0.947, specificity was 0.068, PPV was 0.225 and NPP was 0.818. Accuracy was 0.263. **Conclusion:** The incidence of BRCA1 and BRCA2 deleterious mutations in our study was similar to that found in other populations. NCCN criteria were a poor predictor of deleterious mutation in BRCA1 and BRCA2 in general, although most mutant patients had at least one NCCN testing criteria, specially increasing number of affected relatives and Ashkenazi lineage.

KEYWORDS: Gene; breast cancer; genetics; mutations.

RESUMO

Objetivo: Identificar as mutações genéticas nos genes BRCA1 e BRCA2 em mulheres com suspeita de Síndrome de Câncer de Mama e Ovário Hereditários e correlacioná-las com os critérios de testagem da *National Comprehensive Cancer Network* (NCCN), a fim de verificar o seu impacto nas taxas de achados de mutação, bem como identificar os critérios relevantes, a frequência e o tipo de mutações encontradas e a importância relativa de cada critério da NCCN. **Metodologia:** Desenvolveu-se uma base de dados com todos os casos testados para a Síndrome de Câncer de Mama e Ovário Hereditários pelo segundo autor de 2010 a 2016. As variáveis de interesse foram anotadas e, em seguida, analisadas por meio de um pacote estatístico para encontrar variáveis relevantes. **Resultados:** Um total de 171 pacientes foi testado e 38 apresentavam mutações prejudiciais (22%). Os critérios com uma associação significativa às mutações presentes foram os números totais de parentes com câncer (p=0,02) e a descendência Ashkenazi (p=0,001). A idade do parente mais jovem com câncer abaixo de 49 anos não foi significativa nesta amostra (p=0,1). Houve uma forte correlação entre pacientes com mutações e os critérios da NCCN (p=0,0001), mas não encontramos tal correlação entre a presença de testes de NCCN e a presença de mutação (p=0,11). Com relação ao uso dos critérios da NCCN para encontrar mutações BRCA, a sensibilidade foi de 0,947, a especificidade foi de 0,068, PPV foi de 0,225 e NPP foi de 0,818. A acurácia foi de 0,263. **Conclusão:** A incidência de mutações prejudiciais de BRCA1 e BRCA2 em nosso estudo foi semelhante àquela encontrada em outras populações. Os critérios da NCCN foram preditores fracos de mutação prejudicial no BRCA1 e no BRCA2 no geral, embora a maioria dos pacientes mutantes tenha tido, no mínimo, um critério de teste da NCCN, especialmente aumentando o número de parentes afetados e a descendência Ashkenazi.

PALAVRAS-CHAVE: Genes; câncer de mama; genética; mutações.

INTRODUCTION

Statistics from the National Institute of Cancer (INCA) point out the occurrence of 57,960 new cases of breast cancer in Brazil in 2016, which represents around 28% of all female cancers in the country.[1] Among the risk factors for the development of breast cancer, genetic heritage has surely the biggest impact. A risk indication is the history of the disease in mother or sister – the lower the age at diagnosis, with more cases in the family, the higher the risk for the woman. Several genes of susceptibility to breast cancer have already been characterized and mostly of them are of low penetrance, i.e. they slightly modify the risk for cancer development throughout life (<15%), and they are common in the general population. The so-called genes of moderate penetrance have relatively rare alleles and grant the bearer an increase of moderate risk (15 to 30%).

In this research, we discussed the clinical and genetic aspects of the Hereditary Breast and Ovarian Cancer Syndrome (HBOC) caused by a germinative mutation of high penetrance in the genes BRCA1 and BRCA2; then, we correlated it with the criteria established by the National Comprehensive Cancer Network (NCCN) for testing patients with the syndrome. The aim was to identify, in the Brazilian population, the relevant variables which comply with the genetic testing criteria of patients with HBOC and to identify, in the studied population, the genetic mutations and their frequency. Also, to assess the number of occurrences of mutations found for each NCCN criteria, evaluating its resolution.

According to Yiannakopoulou[2], family groups of cancer correspond to 20 to 30% of the breast cancer cases and they are especially caused by genes of medium and low penetrance; only a small part is caused by genes of high penetrance. Of this last group, BRCA mutations respond to about 75% of the cases. In a recent cohort of 9,856 patients with mutations detected in these genes, the cumulative risk of breast cancer until the age of 80 was of 72% for BRCA1 and 69% for BRCA2, whereas the risk of ovarian cancer was of 44% and 17%, respectively. In addition, we found that the penetration varies according to the location of the variants regarding the *locus* in the gene[3].

There are few prevalence studies of mutations in the BRCA genes in the Brazilian population, which has a highly complex and diversified genetic inheritance. Carraro et al.[4], studying 54 patients with breast cancer diagnosed at the age of 35, found a rate of 20.5% of cases with mutations in the BRCA1 (13%) and BRCA2 (7.5%) genes. Gomes et al.[5] found 2.3% of the cases with mutations in BRCA1 and BRCA2 in a non-selected population of 402 patients with breast cancer.

Database construction

We analyzed the medical records, heredograms and exams results from 171 patients' follow-up from the clinic of Dr. José Claudio Casali da Rocha, during the period between January 2012 and April 2016. We extracted the variables seen in Table 1 that are stored in a database developed specifically for this purpose in the software File Maker Pro 13.

Correlation with NCCN criteria

The annotated variables from each case were assessed based on the criteria from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Breast and Ovarian, version 2.2016 (available at NCCN.org), and signalized according to the recommendation created by this

Table 1. Variables analyzed in the study.

Variable	Variable
Identification	Number of relatives, level of family degree, and type of tumor from relatives.
Date of birth	Associated benign pathologies.
Gender	Performed surgeries.
Lineage	Has been through radiotherapy?
Breast cancer?	Has been through chemotherapy?
Age in the first breast cancer	Has used tamoxifen?
Histology	Has used aromatase inhibitor?
Second synchronic breast cancer?	Has used Herceptin?
Second metachronic breast cancer?	
Bilateral breast cancer?	
Receptors of estrogen, progesterone, Ki67 and HER2	
Ashkenazi?	
Presence of other cancers? Which ones?	
Found mutations	

protocol, in the event they obtained or did not obtain the testing criteria, and by the presence or absence of mutations.

Comparison between the local indication and the NCCN indication

For each case recorded in the database, we made a comparison between the presence, or not, of mutations and the NCCN criteria indicating the testing ("NCCN variable").

1. Cases in which these two variables coincided were signalized as "concordant NCCN".
2. Cases in which the testing was positive and the NCCN criterion for testing was not obtained were annotated as "negative NCCN".
3. Cases in which the testing was negative and the NCCN criterion for testing was obtained were annotated as "positive NCCN".

RESULTS

In the sample of 171 sequenced patients, we found 38 women with pathogenic or probably pathogenic variants. The probably pathogenic variants included were considered significant within the genetic counseling context. The NCCN criteria associated with this finding with statistical significance were the total amount of relatives with cancer (p=0.02) and the Ashkenazi lineage (p=0.001).

We did not find a statistically significant association between the presence of the following NCCN criteria and the presence of pathogenic variants: age of the youngest relative with breast cancer below 49 years old (p=0.1), mean of age in the groups (41.2 years old in the group of pathogenic variants against 42 years old in that without these variants, p=0.4) and presence, or not, of NCCN criteria (36 mutated patients with NCCN criteria and another 2 mutated without any criteria, p=0.11).

Table 2 lists the pathogenic or probably pathogenic variants found in 38 patients.

DISCUSSION

We need to develop criteria for indicating proper genetic testing to the Brazilian reality from the scientific point of view, identifying the genetic syndromes and their most frequent associated mutations in Brazil within a context of genetic counseling based on heredogram. Also from the social point of view, to identify the relevance and impact that the identification of these mutations will have on our population, especially in that part covered by the public health. Based on the scarce availability of resources for health actions in the public service (without forgetting the same problem in the supplemental health), we have been introduced to a problem that is analogous to that discussed, for instance, establishment of limits to the mammographic screening. Is it viable, in terms of public health, to extend the annual screening

after the 70 years? Does the decrease of treatment morbidity and overall survival obtained through this tracking overcome the investment that is not done in other areas? If we reflect upon the coverage for genetic testing in Brazil, we will powerfully have to make the same choices. Is it worth to test all patients younger than 60 years with triple negative tumors as pointed out by the NCCN criteria, adopted in a society where the economic relations in health are completely different? What will be the impact of this testing in the morbidity and mortality of our patients and their families? In order to achieve the capacity of assessing all of these questions, based on solid scientific evidence, we need to hugely advance in the hereditary cancer epidemiology in our country, which depends on clinical research investment – something that does not seem a possible reality in a close horizon. Clearly, the moment requires a joined assessment of the genetic and mastology societies in a way to establish a consensus on which criteria should we import and support, considering the theoretical knowledge obtained in developed countries and in our socioeconomic reality.

The genetic syndromes of hereditary breast cancer, of which the HBOC is the main representative, have as basic characteristic being dominant autosomal inheritance syndromes. Therefore, we should not forget that the main criterion for diagnosing these syndromes continues to be family history, represented visually by the heredogram which, thus, is still an essential tool for making decisions. The other NCCN criteria (like age and histology) may be considered presumption criteria in the absence of a significant heredogram. We may indicate preventive measurements based only on the heredogram, in the event of no possibility of genetic sequencing, but only within a context of genetic counseling carried out by a properly trained professional. Hence, not only this kind of indication is possible but also the opposite, i.e. the counterindication of aggressive preventive measurements even in the presence of known pathogenic variants. The awareness of this fact has a remarkable social importance, especially in a society that is economically poor as ours, and it allows providing medicine with better quality, even in the absence of technological resources. This discussion, however, should not be considered an approval to aggressive preventive attitudes that are habitual and routinely conducted only with clinical indication. It should also be considered a possible attitude of exception to be adopted by a skilled professional in the absence of genetic sequencing possibility, which is still the gold standard in the determination of known hereditary cancer syndromes.

In order to reflect on the importance of what we have just discussed, consider an analysis of the prevalence table of pathogenic variants in BRCA1 and BRCA2 in non-Ashkenazi women – available at Myriad[6] website, which probably has the greatest accumulation of data in the planet. It is worth noting this company was, a few years ago, the holder of the "patent" of BRCA genes (Prevalence Tables of Deleterious Mutations in BRCA1 and BRCA2 n.d.)[6].

Table 2. Found variants.

Gene/transcribed	Classification	Frequency	Protein	Mollecular consequence	Variation	dbSNP
BRCA1_NM_007294.3	Possibily pathogenic	0.00247%	p.Leu1844Arg	Missense	Single nucleotide variant	rs80357323
BRCA1_NM_007294.3	Pathogenic	413,000%	p.Gln563Ter	Nonsense	Single nucleotide variant	rs80356898
BRCA1_NM_007294.3	Pathogenic	0.1565%	p.Gln1756Profs	Frameshift	Duplication	rs80357906
BRCA1_NM_007294.3	Pathogenic	0.00082%	p.Ser1655Tyrfs	Frameshift	Deletion	rs80359876
BRCA1_NM_007294.3	Pathogenic	0.001%	p.Arg71Gly	Missense	Single nucleotide variant	rs80357382
BRCA1_NM_007294.3	Pathogenic	0.001%	p.Ser1389Terfs	Frameshift	Deletion	rs80357572
BRCA1_NM_007294.3	Pathogenic		p.Ser1655Phe	Missense	Single nucleotide variant	rs80357390
BRCA1_NM_007294.3	Pathogenic	0.024%	p.Glu23Valfs	Frameshift	Deletion	rs386833395
BRCA1_NM_007294.3	Pathogenic		p.Trp1782Ter	Nonsense	Single nucleotide variant	rs80357219
BRCA1_NM_007294.3	Pathogenic		p.Gln1111Asnfs	Frameshift	Deletion	rs80357701
BRCA1_NM_007294.3	Pathogenic			Intron variant	Single nucleotide variant	rs80358050
BRCA1_NM_007294.3	Pathogenic			Splice acceptor variant	Single nucleotide variant	rs80358054
BRCA2_NM_000059.3	Pathogenic	0.001%	p.Met1Arg	Missense	Single nucleotide variant	rs80358547
BRCA2_NM_000059.3	Pathogenic	0.001683%	p.Lys2162Asnfs	Frameshift	Deletion	rs80359598
BRCA2_NM_000059.3	Possibily pathogenic			Splice acceptor variant	Single nucleotide variant	rs397507404
BRCA2_NM_000059.3	Pathogenic	0.002%	p.Ala938Profs	Frameshift	Deletion	rs80359351
BRCA2_NM_000059.3	Benign	0.325%	p.Arg2034Cys	Missense	Single nucleotide variant	rs1799954
BRCA2_NM_000059.3	Pathogenic	0.027%	p.Ser1982Argfs	Frameshift	Deletion	rs80359550
BRCA2_NM_000059.3	Pathogenic		p.Ser2219Ter	Nonsense	Single nucleotide variant	rs80358893
BRCA2_NM_000059.3	Pathogenic	0.002%	p.Ala938Profs	Frameshift	Deletion	rs80359351
BRCA2_NM_000059.3	Pathogenic		p.Asn1603Thrfs	Frameshift	Deletion	rs397507743
BRCA2_NM_000059.3	Pathogenic		p.Tyr3049Ter	Nonsense	Single nucleotide variant	rs886040823
BRCA2_NM_000059.3	Possibily pathogenic	0.00239%		Deleção	Point mutation	rs276174816
BRIP1 NM 032043.2	Pathogenic		p.Trp647Cys	Missense	Point mutation	rs786202760
FANCM NM 020937.3	Possibily pathogenic		p.Leu1950Val	Missense	Point mutation	rs146436929
BRCA2_NM_000059.3	Possibily pathogenic			Missense	Point mutation	rs81002875
BRCA1 Gene complete deletion	Pathogenic				Deletion	
BRCA1 Gene complete deletion	Pathogenic				Deletion	
BRCA2 Undescribed	Possibily pathogenic		p.L2253fs	Frameshift	Deletion	
BRCA2 Undescribed	Possibily pathogenic			Deleção	Point mutation	
BRCA1 Undescribed	Possibily pathogenic			Nonsense	Point mutation	
BRCA1 Undescribed	Possibily pathogenic			Missense	Point mutation	
BRCA2 Undescribed	Possibily pathogenic			Nonsense	Point mutation	
BRCA2 Undescribed	Possibily pathogenic		p.Ser723Leu	Nonsense	Point mutation	
BRCA1 Undescribed	Possibily pathogenic			Missense (splincing)	Point mutation	
BRCA1 Undescribed	Possibily pathogenic			Missense (splincing)	Point mutation	

The only groups with prevalence of pathogenic variants above 40% are those in which there is the presence of ovarian cancer in the proband's family; in the absence of occurrence (in the patient or in a close relative), the prevalence of pathogenic variants is of 21% at most.

Some limitations in our research should be pointed out, because they affect the level of certainty of the obtained conclusions.

The presence of ovarian cancer was low in the sample and did not allow the relevance of this criterion, which, in more robust samples, is always more important in the assumption of the HBOC presence. Also as a function of the sample size, the presence of two mutated patients without NCCN criterion was responsible for the non-statistical significance of the NCCN criteria presence.

CONCLUSION

The incidence of pathogenic variants in the BRCA1 and BRCA2 genes was similar to that found in other studies. The NCCN criteria were poor predictors of the presence of pathogenic variants in the BRCA1 and BRCA2 genes, although most of the pathogenic covariant patients had at least one NCCN criterion, especially a higher number of relatives with cancer and Ashkenazi ascendency.

REFERENCES

1. Brasil. Instituto Nacional de Câncer (INCA). Estimativa 2016 [Internet]. 2016 [cited 2017 June 26]. Available from: http://www.inca.gov.br/estimativa/2016/sintese-de-resultados-comentarios.asp

2. Yiannakopoulou E. Etiology of familial breast câncer with undetected BRCA1 and BRCA2 mutations: clinical implications. Cell Oncol (Dordr). 2014;37(1):1-8. DOI: 10.1007/s13402-013-0158-0

3. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast câncer for BRCA1 and BRCA2 mutation carriers. JAMA. 2017;317(23):2402-16. DOI: 10.1001/jama.2017.7112

4. Carraro DM, Folgueira MA, Lisboa BC, Olivieri EH, Krepischi AC, Carvalho AF, et al. Comprehensive analysis of BRCA1, BRCA2 and TP53 germline mutation and tumor characterization: a portrait of early-onset breast cancer in Brazil. PLoS One. 2013;8(3):e57581. DOI: 10.1371/journal.pone.0057581

5. Gomes MC, Costa MM, Borojevic R, Monteiro AN, Vieira R, Koifman S, et al. Prevalence of BRCA1 and BRCA2 mutations in breast cancer patients from Brazil. Breast Cancer Res Treat. 2007;103(3):349-53.

6. Myriad. Prevalence tables of deleterious mutations in BRCA1 and BRCA2 [Internet]. [cited 2017 June 26]. Available from: http://myriadgenetics.eu/healthcare-professional-treating-diseases/hereditary-cancer-testing/hereditary-breast-and-ovarian-cancer-hboc-syndrom/prevalence-tables/

INVASIVE TRIPLE NEGATIVE BREAST CANCER WITH BASAL AND NON-BASAL-LIKE IMMUNOPHENOTYPES: PROGNOSTIC IMPLICATIONS

Carcinoma invasivo de mama triplo negativo com imunofenótipo basal e não basal: implicações prognósticas

Darley de Lima Ferreira Filho[1]*, Nancy Cristina Ferraz de Lucena Ferreira[1], Maria do Carmo Abreu e Lima[2], Alvaro Antonio Bandeira Ferraz[2], Danyelly Bruneska Gondim Martins[2,3], Thais de Lucena Ferreira[4]

ABSTRACT

Objectives: The objective of the study was to compare the postoperative staging and clinical development outcomes in a period of three years with the histopathological and immunohistochemical characteristics considered prognostic and/or predictive factors in patients being treated for triple negative type of breast cancer in the Barão Lucena Hospital, Recife, Pernambuco. **Method:** The study was conducted with 125 female patients suffering from triple negative breast cancer who underwent surgical treatment in the mastology service of Barão Lucena Hospital from 2009 to 2012. The clinical and pathological features of the tumors were studied and correlated with basal and non-basal subtypes. A descriptive data analysis was carried out using tables and/or graphs for qualitative variables. Association analysis was performed using χ^2 test for independence. In tables that showed expected frequency lower than 5, in more than 20% of cells, we used the Fisher's exact test. In addition, the odds ratio (OR) and the confidence interval (CI) for OR were calculated. In the entire analysis, a 5% significance level was considered. **Results:** Mean age was 49 years; regarding race, black was present in 83 (66.4%). The most common histological type was ductal, in 111 (88.8%). The pathological stage I/II was the most common, in 87 (69.6%) patients. A total of 71 patients (56.8%) showed no axillary metastasis. Regarding the type of surgery, the conservative one was performed in 57 (45.6%), including sectorectomy and oncoplastic surgery. The recurrence was present in 30 patients, basal in 16 (53.3%) patients and 14 (46.7%) in the non-basal, and bone metastasis was the most frequent. **Conclusion:** In this triple-negative tumor sample, the most important facts related to survival were: being aged less than 40 years, histological type, cytokeratin CK5/6 and higher significance level of the factors EGFR and KI-67.

KEYWORDS: Triple negative breast neoplasms; breast; breast neoplasms.

RESUMO

Objetivos: O objetivo do estudo foi correlacionar o estadiamento pós-cirúrgico e a evolução clínica em um período de três anos com as características histopatológicas e imunoistoquímicas consideradas fatores prognósticos e/ou preditivos nas pacientes em tratamento de câncer de mama do tipo triplo negativo do Hospital Barão de Lucena, Recife, Pernambuco. **Método:** O estudo foi feito com 125 pacientes do sexo feminino portadoras de câncer de mama triplo negativo e que foram submetidas a tratamento cirúrgico no serviço de mastologia do Hospital Barão de Lucena no período de 2009 a 2012. Nessas pacientes foram estudadas as características clínicas e patológicas dos tumores, as quais foram correlacionadas com os subtipos basal e não basal. A análise descritiva dos dados foi feita através de tabelas e/ou gráficos para variáveis qualitativas. Para análise de associação, foi utilizado o teste do χ^2 para independência. Nas tabelas que apresentaram frequência esperada menor que 5, em mais de 20% das caselas, foi utilizado o teste exato de Fisher. Além disso, foi calculada a razão de chance (OR) e o intervalo de confiança (IC) para OR. Em toda a análise foi considerado nível de significância de 5%. **Resultados:** A média de idade foi de 49 anos; com relação à raça, tivemos a cor negra em 83 (66,4%) delas. O tipo histológico mais comum foi o ductal, em 111 (88,8%) pacientes. O estágio patológico I/II foi o mais comum, em 87 (69,6%) delas. Um total de 71 (56,8%) pacientes não demonstrou comprometimento axilar. Com relação ao tipo de cirurgia, a conservadora foi utilizada em 57 (45,6%) pacientes, incluindo setorectomia e técnicas de oncoplastia. A recorrência esteve presente em 30 pacientes, sendo basal em 16 (53,3%) e não basal 14 (46,7%) delas, nas quais a metástase óssea foi a mais frequente. **Conclusão:** Nessa amostra de tumores triplo negativo, os fatos mais importantes associados à sobrevida foram a idade abaixo de 40 anos, o tipo histológico, a citoqueratina CK5/6 e o grau de significância maior dos fatores EGFR e KI-67.

PALAVRAS-CHAVE: Câncer de mama triplo negativo; mama; neoplasias da mama.

INTRODUCTION

Breast cancer is the global leader in terms of incidence and mortality among women. This disease has been increasing every year. In the past few years, studies have had great evolution, however, the problem is still devastating. The number of cancer cases has been growing all over the world. However, the incidence of this disease and the mortality resulting from it present relevant differences according to geographic regions[1].

The occurrence of 1 million cases of breast cancer is estimated in the next few years, and the development of the disease in more than 9% of the female population in the world. Most cases occurs in developed countries, and the Netherlands has the highest incidence (90.2/100 thousand), followed by the United States (86.9/100 thousand). About 1 out of 8 American women (about 12%) will present with invasive breast cancer throughout their lives. According to the report by the World Health Organization (WHO), global mortality in 2007 was of about 548 thousand deaths, of which 72% took place in underdeveloped or developing countries. In these countries, both the incidence and the mortality increased considerably due to population aging, changes in reproductive patterns, higher exposure to risk factors and problems related with the opportune access to early detection and diagnosis, as well as adequate treatment[2].

The early detection of breast cancer is a decisive factor in the determination of prognosis. Epidemiological studies in different Brazilian regions are important for the development of better prevention and screening programs.

They are characterized as heterogeneous neoplasms, with several histopathological subtypes, besides different clinical presentations with several variations in terms of response to treatment[3,4]. One of the major challenge for the study and treatment of the breast carcinoma is its tumoral heterogeneity[5]. The current classification of invasive breast carcinomas by the WHO is histological and presents an extensive list, of which the most common histological types are the invasive ductal carcinoma (50 to 75%) and the invasive lobular carcinoma (5 to 15%). The others, considered special types, are less frequent and include the tubular, mucinous, medullary and metaplastic carcinoma, among others[6].

The level of histological differentiation is also a measure of great utility in the clinic, and reflects the malignant potential of the tumor indicating its higher or lower capacity for metastization. The anatomopathological classification is insufficient to characterize the breast carcinomas, once tumors with the same level, stage and histological type may present with different prognosis and response to therapy[7].

There are factors involved in the prognostic evaluation of breast cancer, and it is important to consider size, type and histological grading, vascular invasion, lymphatic ganglia involvement, cell proliferation index, and expression of hormone receptors and negative epidermal growth factor (HER-2) receptors. The classification of breast carcinomas in molecular types is based on changes in some genes. With the immunohistochemical profile, we managed to obtain an indirect approximation of these subgroups, using luminal A, luminal B, HER-2 and triple negatives.

Due to the heterogeneity of the tumor types and their morphological and phenotypic traits, it is difficult to establish a relationship between the clinical findings, the prognoses and the level of recurrence that may occur with the years, after the adjuvant treatment. In our region, there are no institutional studies correlating the triple-negative tumors with the basal and non-basal like immunophenotype, with their probable prognostic implications.

METHODOLOGY

The study was carried out with 125 patients with triple-negative breast cancer of a total of 830 who were submitted to clinical and surgical treatment in the mastology service of Hospital Barão de Lucena, from July, 2009, to July, 2012. The patients were followed-up for a three-year period, when the type of treatment, recurrences and clinical and pathological characteristics of the tumors were assessed.

To interpret the negative results of HER-2, we used the 0 to 1+ score, considering as positive the tumors presenting with intense color (3+), in the entire cell membrane, in more than 30% of the assessed cells. The 0 score does not show cell membrane coloring, or is present in less than 10% of the tumor cells. Score 1+ showed slight or incomplete coloring of the membrane in more than 10% of the tumor cells[8]. The hormone receptors were considered negative when there was less than 1% and absence of expression of estrogen receptors (ER), or less than 1% of colored nuclei, according to the consensus by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP)[9].

To define the basal-like immunophenotype, we complemented the panel with the CK5/6 markers (Clone D5/16B4:DAKO) and epidermal growth factor receptor (EGFR) (Clone 31G7). According to the literature, the basal-like immunophenotype is based on the triple negativity for hormone receptors and HER-2. This hypothesis can be assessed with other markers based on clinical criterion. The core-basal designated immunophenotype (triple-negative invasive breast carcinoma positive for CK5/6 or EGFR) can be used as a predictor of the basal-like genetic molecular profile, with 76% sensitivity and 100% specificity.

The basal-like immunophenotype (CK5/6 and/or positive EGFR) was observed in 81 (64.8%) cases, and in 44 (35.2%) cases, the basal-like was not confirmed by the immunophenotype (negative CK5/6; negative EGFR). In the 81 cases with basal-like immunophenotype, 49 (60.4%) were positive for CK5/6, and 76 (93.8%) for EGFR; 44 (34.3%) presented both markers.

The descriptive data analysis was carried out using tables and/or graphs for qualitative variables. The χ^2 test of Independence was used to analyze the association. In tables presenting expected frequencies lower than 5, in more than 20% of the cells, Fisher's exact test was used. Besides, the odds ratio (OR) and the confidence interval for the OR were calculated. The 5% significance level was considered in the entire analysis. Regarding the prognostic factors determined by the immunohistochemical examination, the patients were divided in two groups: basal and non-basal. The Wald's test was used as a logistic regression model to evaluate EGFR and KI-67 according to personal and clinical factors of the patients. The tests Log Rank, Breslow and Tarone-ware were used to compare the analysis of survival, in order to obtain better statistical evaluation (Table 1).

Table 1. Distribution of frequency of the personal and clinical profiles of the patients, and contingency table with the subtype of the carcinoma.

Factor assessed	Subtype		P-value
	Basal-like (%)	Non-basal like (%)	
Age (years)			
<35	4 (100.0)	–	
35 to 45	23 (59.0)	16 (41.0)	0.175[b]
46 to 59	27 (58.7)	19 (41.3)	
60 or more	27 (75.0)	9 (25.0)	
Color			
Black	52 (62.7)	31 (37.3)	0.479[a]
White	29 (69.0)	13 (31.0)	
CK5/6			
Positive	49 (96.1)	2 (3.9)	<0.001[a]
Negative	32 (43.2)	42 (56.8)	
EGFR			
Positive	76 (97.4)	2 (2.6)	<0.001[a]
Negative	5 (10.6)	42 (89.4)	
KI-67			
Minimum	15	10	–
Maximum	90	80	–
Mean±standard-deviation	58.8±17.3	30.6±18.8	<0.001[c]
Type of surgery			
Mastectomy	45 (66.2)	23 (33.8)	
Sectorectomy	9 (64.3)	5 (35.7)	
Oncoplastic surgery	12 (57.1)	9 (42.9)	0.920[b]
Sectorectomy +AD	5 (62.5)	3 (37.5)	
Sectorectomy+SL	10 (71.4)	4 (28.6)	
Presence of metastasis			
Yes	16 (53.3)	14 (46.7)	0.131[a]
No	65 (68.4)	30 (31.6)	
Pathological staging			
I	12 (57.1)	9 (42.9)	
II	43 (65.2)	23 (34.8)	0.683[a]
III	26 (68.4)	12 (31.6)	
Histology			
Ductal	73 (65.8)	38 (34.2)	
Lobular	5 (62.5)	3 (37.5)	0,746[b]
Others	3 (50.0)	3 (50.0)	
Histological Type			
I	11 (57.9)	8 (42.1)	
II	13 (50.0)	13 (50.0)	0,002[a]
III	44 (86.3)	7 (13.7)	
Lymph nodes			
0	43 (60.6)	28 (39.4)	
1 a 3	13 (65.0)	7 (35.0)	0,615[a]
4 a 9	15 (71.4)	6 (28.6)	
10 ou mais	10 (76.9)	3 (23.1)	

EGFR: epidermal growth factor receptor; [a]p test of the χ^2 test (if p-value<0.05, the factor assessed influences the subtype of the carcinoma); [b]p-value of Fisher's Exact Test; [c]p-value of the Student's t test (if p-value <0.05, the means of both groups are significantly different); AD: axillary dissection; SL: sentinel lymph node.

RESULTS

The profiles of the triple-negative basal and non-basal like tumors were correlated with the following variables: age, skin color, histological type, pathological staging, number of compromised lymph nodes, CK5/6, EGFR, KI-67, type of surgical procedure (mastectomy, sectorectomy, with axillary or sentinel lymph node dissection, breast reconstruction) and recurrence (present or absent).

The patients were aged in average 49.77 years. The distribution of patients as to age group was: up to 35 years, 4 patients (4%); between 35 and 45 years, 39 patients (31.2%); between 46 and 59 years (36.8%); and 33 patients (28.8%) were older than 60. When these data were associated, the basal-like subtype was more prevalent in the group aged less than 35 years, and the non-basal like, in the age group of 41 to 50 years.

Regarding skin color, 52 patients (62.7%) were black, and 29 patients (69.0%) were white in the basal-like subtype. In the non-basal like subtype, the black color was found in 31 patients (37.3%), and white in 13 (31.0%).

The most common histological type was the invasive ductal carcinoma (IDC), which occurred in 111 patients (88.8%), followed by the invasive lobular carcinoma (ILC), in 8 patients (6.4%). The other types of carcinoma were medullary, tubular and mucinous, which occurred in only 6 patients (4.8%). The histological type in the basal-like subtype represented 65.8%, and in the non-basal like, 34.2%.

Regarding pathologic staging, stage I was found in 21 patients, representing 16.8%; stage II was the most present, corresponding to 66 patients (52.8%); followed by stage III< in 38 patients (30.4%). Both in basal and in non-basal like, pathologic stage II was the most prevalent one, being found in 43 (65.2%) and 23 (34.8%) patients, respectively. There was absence of axillary involvement in 71 patients (56.8%); from 1 to 3 involved lymph nodes, in 20 (16.0%); from 4 to 9 lymph nodes, in 21 (16.8%); and above 10 lymph nodes, in 13 patients (10.4%). The patients with more than ten lymph nodes compromised were associated with the basal-like subtype. In the basal and non-basal like subtypes, the absence of axillary involvement was the most present in both groups (Figure 1).

As to surgical procedure, the most frequent type of surgery was radical mastectomy (54.4%), in 68 patients. The conservative surgery with sectorectomy, using oncoplastic techniques, occurred in 57 patients (45.6%).

In the analysis of the 125 patients, we observed that in 81 (64.8%) cases, the basal-like immunophenotype was confirmed (CK5/6 and/or positive EGFR), and in 44 (35.2%), basal-like was not confirmed by the immunophenotype (negative CK5/6; negative EGFR). In the 81 cases with basal-like immunophenotype, 49 (60.4%) were positive for CK5/6, and 76 (93.8%), for EGFR (Figures 2 and 3).

The histological type, divided in three groups (I, II and III), is an important prognostic factor in triple negatives. Type I was found in 19 patients (19.8%); type II, in 26 (27.1), and type III, in 51 (53.1%). In basal-like, type III was the most frequent (86.3%), and, in non-basal like, it occurred in 13.7% (p<0.002).

We observed the adjustment of the logistic model for the subtype according to personal and clinical factors of the patients. It was observed that only EGFR and the value of KI-67 were significant together for the subtype. Also, it was observed that EGFR remains in the model as a correction factor (p=0.996), and only KI-67 was significant (p=0.022). Besides, the KI-67 growth in one unit increases the chances of the patient presenting with the basal-like subtype in 7% (Table 2).
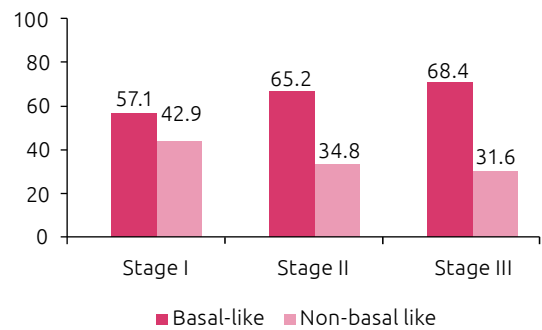
Figure 1. Distribution of patient according to pathological staging and subtype.
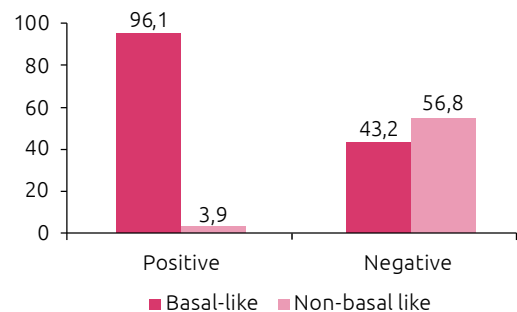
Figure 2. Distribution of patients according to CK5/6 situation and subtype.
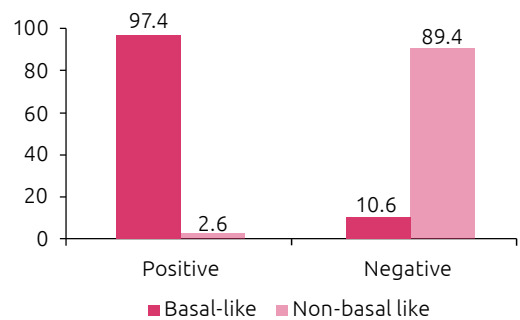
Figure 3. Distribution of patients according to epidermal growth factor receptor situation and subtype.

Table 3 shows the comparison tests between the personal and clinical profile of these patients and survival. It was possible to observe that color, CK5/6, type of surgery, presence of metastasis, histology and histological type are not statistically significant variables for the survival of patients in our study. The factors of age, EGFR, and pathologic staging were significant to determine the survival of the patient, who were assessed for 36 months.

The survival curve shows these data. It is important to mention that the presence of metastasis and the histological type were very close to significance in the three tests applied, indicating there is a tendency of these variables to influence on the survival of the patient (Figures 4, 5 and 6).

Regarding recurrence, 30 (24.0%) patients had metastasis, of whom 16 belonged to the basal-like group (53.3%), and 15 (46.7%), to the non-basal like group. Thirty patients presented with metastasis (16.26%), and 95 patients did not (83.74%). In patients with metastasis, the bone form was the most common, in 11 patients

Figure 4. Analysis of survival of the patients according to age group.

Table 2. Logistic model for the subtype according to personal and clinical factors of the patients.

Factor assessed	OR	CI	P-value[a]
EGFR			
Positive	5.58×10^9	*	0.996
Negative	1.00	–	
KI-67	1.07	1.01–1.13	0.022

OR: *odds ratio*; CI: confidence interval; EGFR: epidermal growth factor receptor; [a]p-value of the Wald's test (if p<0.05, the assessed factor is determinant for the basal-like subtype); *it was not possible to calculate the confidence interval.

Table 3. P value of the survival comparison tests between the personal and clinical profile of the assessed patients.

Factor assessed	P value of the test			
	Log rank	Breslow	Tarone-ware	Wald
Age	0.010	0.003	0.005	–
Color	0.211	0.125	0.160	–
CK5/6	0.137	0.146	0.140	–
EGFR	0.024	0.027	0.025	–
KI-67	–	–	–	0.405
Type of surgery	0.657	0.667	0.659	–
Presence of metastasis	0.083	0.040	0.056	–
Pathological staging	0.036	0.038	0.036	–
Lymph node involvement	0.632	0.690	0.670	–
Histology	0.134	0.073	0.097	–
Histological type	0.410	0.410	0.410	–

EGFR: epidermal growth factor receptor.

Figure 5. Anaysis of survival of patients according to epidermal growth factor receptor.

(5.2%); followed by pleural-lung metastasis, in 6 patients (2.84%). There were two deaths in the three-year follow-up period, one caused by meningeal and brain metastasis.

The figures show the graphic representation of the factors that had the most statistical significance for the evaluated patients.

DISCUSSION

The natural history of triple-negative breast is not clear, since its evolution does not take place in a uniform manner in all women, being very heterogeneous. Because of this behavioral divergence in relation to some tumors that present the same clinical characteristics, it is important to analyze more prognostic factors that involve its general context. Triple-negative tumors have different epidemiological characteristics, as well as the behavior and evolution of the basal-like and non-basal like subtype. Therefore, besides the diagnosis of the disease itself, there are clinical and biological aspects associated with the differences of disease-free and global survival time[10,11].

The appropriate identification of prognostic factors and the predictive responsive parameters to a specific treatment are still challenges in the individualization of the best therapy for each patient[12]. A series of recommendations for the selection of adjuvant

Pathological staging

⌐ I	+ I-censored		
⌐ II	+ II-censored		
⌐ III	+ III-censored		

Figure 6. Analysis of survival of patients according to pathological staging.

systemic therapies for triple-negative basal and non-basal like tumors has been recently proposed in the 14th International Conference on Adjuvant Therapy of Primary Breast Cancer, in Saint Gallen, Switzerland[13].

The increased expression of some of these biological substances can be present in malignant breast neoplasms, presenting relevance from the prognostic point of view. The most important biological factors are the estrogen and progesterone hormone receptors, the expression of the anomalous protein p53 and the amplification of the oncogene HER02, as is the absence of hormone and HER-2/neu protein receptors[14].

The patient's age at the time of diagnosis is important, since it is directly related with the menopausal status, and, consequently, with the hormone action in tumor growth. Older women, in post-menopause, with breast cancer present increasing concentration of ER in the tumor, and their cancers are usually well differentiated, with low rates of proliferation[15]. However, in younger women, it is common to find triple-negative and poorly differentiated tumors. In our study, we observed that mean age was 45 years, in a pre-menopausal stage, in which 46 patients were aged between 46 and 59 years, above the average found in the literature, which presents higher frequency below the age of 40. Van Belle et al.[16], in a survey, showed mean age of 40 years. Studies demonstrated that younger women have worse prognosis in relation to older women, in post-menopause[17]. Large tumors, ganglion involvement, negative for ER, increased phase S and p53 abnormality are very common at the age of 30 to 35 years[15]. In our sample, patients aged less than 40 years, in 27 cases, represented 33.7% of the sample, showing increasing presence of breast cancer in younger patients, possibly due to changes in the lifestyle of the modern woman[18]. Studies with multivariate analysis concluded that younger women have worse prognosis, with increasing risk of recurrence and death[19]. The correlation with the basal and non-basal like subtype presented non-significant p in the examined patients. In our sample, there was no change in prognosis in the two triple-negative subtypes (p=0.175); however, in the studies by Slamon et al.[20], Dati et al.[21], Clark[22] and in the analysis by Farzadnia et al.[23], there was no correlation between age and hormone receptor factors and the HER-2 protein.

Regarding race, the literature shows that women with African American ancestors are in a more advanced stage, with higher mortality index in comparison to white women[24]. Other authors have shown that black or Hispanic patients present with advanced tumors, positive lymph nodes at diagnosis and factors indicating more biological aggressiveness, with negative receptors and high level of proliferation[25]. A higher number of cancer cases is observed in black women, in comparison to white women, in patients aged less than 40 years, and normally present with higher nuclear grade, do not usually have hormone receptors, are
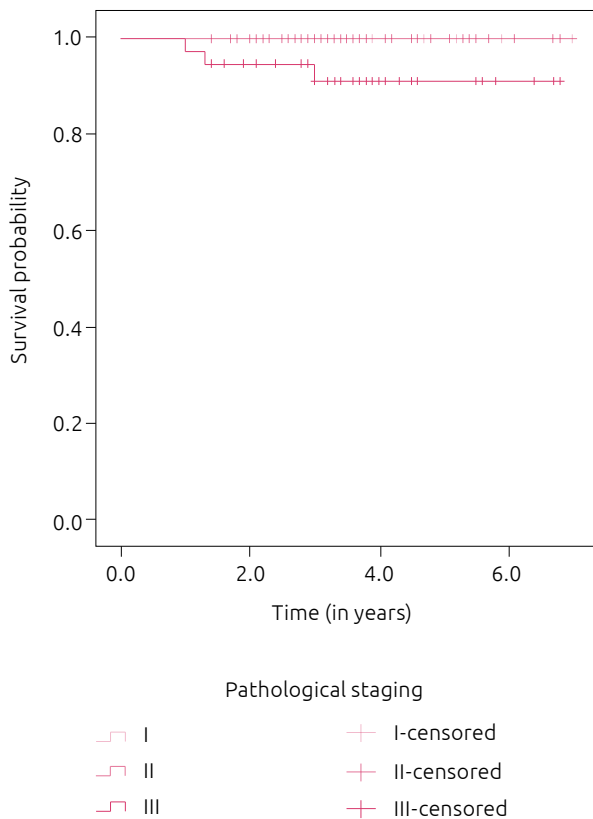
negative for the HER-2 protein and suffer with different types of sporadic p53 mutations[26]. In our study, the black race was mostly affected, constituting 83 cases (66.4%). There is high prevalence of triple-negative tumors in young, black patients[27]. Our sample showed that triple-negative tumors in black patients were found, as the basal-like subtype, in 52 of them (62.7%), and non-basal like, in 31 patients (37.3%), presenting higher prevalence in the white patients. A study conducted in our country by Carvalho et al. in 2014[28] found differences in the molecular subtypes in the several regions of Brazil. The North region had higher incidence of triple-negative (20.3%), with higher African influence (77.8%), when compared to the Northeast (65.5%), and the Center-West (65.9%). In the South and Southeast regions, this incidence is lower.

The invasive ductal carcinomas have worse prognosis, higher incidence of axillary involvement, and constitute most breast invasive carcinomas, corresponding to about 80% of the cases[29]. In our sample, the ductal histological type was found in 111 patients (88.8%). The 30-year survival rate for women with special types of invasive carcinomas (tubular, mucinous, medullary, lobular and papillary) is higher than 60% in comparison to less than 20% in women with the common invasive ductal carcinoma[29]. Among the special histological types, the pure papillary, tubular and mucinous carcinomas, which appear in approximately 2% of the cases, present with the best prognosis[30]. In the sample, the special types were found in only 6 patients (4.8%). The invasive lobular carcinoma, which appears in approximately 10% of the cases, presents different biological and clinical characteristics, since it affects older patients; it is a larger tumor, with higher immunoexpression for ER or progesterone receptor (PR), associated with fraction of the low S phase, with negative HER-2, p53 and EGFR[31,32]. The lobular carcinoma was found in 8 patients (6.4%), but, due to the small number of cases, it was not possible to verify an association with the basal and non-basal like subtypes. There is a direct correlation between tumor size, axillary involvement and level of recurrence of the disease. The tumor diameter is the second prognostic factor in level of importance, and is independent of the condition of the lymph node[28]. Many studies have shown a relationship between tumor size and survival[33]. The survival rate of women with tumors smaller than 1 cm in 10 years is approximately 90%. On the other hand, more than half of the women with tumors larger than 2 cm will have higher chances of lymph node involvement, and many will die[28]. The mean size found in our sample was 3.79 cm, similarly to what was found by Uemura et al[35]. The stage II tumors were found in 96 patients (46.19%) and those considered as stage I, in 62 patients (29.04%). It is possible that tumors that grow too fast in size, without lymph node metastasis, have low chances of distant metastasis[36,37]. We can observe that more than 70% of the tumors were found at initial stages, which enabled conservative, less mutilating surgeries. In a different direction, Bacha et al.[38] found a relationship of the different immunophenotypes (Re, Rp and HER-2) with sizes of tumors III and IV.

Regarding pathological staging, stage I was found in 21 patients (16.8%), stage II corresponded to 66 patients (52.8%), and stage III, in 38 (30.4%). By correlating the basal and non-basal like subtypes, no relationship was found. On the other hand, Mattes et al. in 2014[37] found stage I in 67.2%, followed by stage II, with 286%, in different molecular subtypes. The observation was that triple-negative tumors have low risk of axillary involvement, unlike positive hormone receptors and HER-2, which have high rates of lymph node involvement. Farzadnia et al.[23] did not find correlation between the worst tumor stage and the immunophenotype of HER-2. In the studies by Yuan[39] and Imoto[40], there was correlation between tumor size and proto-oncogene HER-2. In another survey, carried out by Richi and Junqueira[41], there was no statistically significant relation between morphological (tumor size, type and histological grading) or molecular factors (ER/PR/HER-2/KI-67/p53) and the occurrence of metastasis. They established there is a continuous relationship between slow-growing tumors, late axillary lymph node involvement, and more aggressive tumors, with early metastasis to the axilla[42].

The occurrence of metastasis in axillary lymph nodes is considered the most powerful and independent parameter of breast cancer prognosis, in the absence of distant metastasis[43,44]. Axillary involvement is indication for adjuvant systemic therapy. In patient with negative axillary lymph nodes, it is important to assess other prognostic factors, such as tumor size, histological grading, hormone receptors, patient's age and some cell proliferation markers to determine therapy[45]. When the lymph nodes are free of neoplasm, the disease-free survival rate in 10 years is of approximately 70 to 80%; in patients with 1 to 3 involved lymph nodes, it is 35 to 40%; and those with more than 10 lymph nodes involved, it is 10 to 15%. The 5-year survival for patients with negative axilla is 82%, in comparison to 45% for patient with 4 to 12 involved lymph nodes, according to the National Surgical Adjuvant Breast and Bowel Project (NSABP). The use of a sentinel lymph node biopsy is an alternative for the axilla approach, without increasing the costs and preventing the complications of axillary dissection[43]. Regarding the nummber of lymph nodes involved in our survey, most of our patients, 71 (56.8%) did not have axillary involvement; followed by 1 to 3 lymph nodes involved, in 20 patients (16.0%). In those patients who had between 4 and 9 lymph nodes involved, 21 (16.8%), and in patients with more than 10 lymph nodes, 13 (10.4%); there was no association with the basal and non-basal like subtypes. Bacha et al.[38] verified, in patients who had more than 10 lymph nodes involved, a correlation with positive HER-2, with statistically significant finding (p=0.044). In the studies by Wang et al.[46] and Curiliano et al.[47], there was significant relation between the cases with negative receptors and positive HER-2 and positive axilla (p=0.039).

We observed that the mastectomy surgery was used in 68 patients (54.4%), conservative surgery with sentinel lymph node or axillary dissection, in 36 patients (28.8%), and oncoplastic techniques, in 21 (16.8%). These data demonstrate the occurrence of more mutilating surgeries, however, with very interesting balance between mastectomy and conservative surgery in our area, especially due to the increasing rates of early diagnosis of breast cancer. The use of oncoplastic techniques, in many cases, aims at the minimum treatment with maximum effect, always respecting the principles of the classic oncological surgery. With these results, we believe that, in the future, conservative surgeries will overcome radical ones, with the use of oncoplastic techniques. Differently, in the study by Vallejos et al.,[48] with a total of 1,198 patients with breast cancer, about 70 to 75% of the them had radical mastectomy, and the rest underwent conservative surgery. In the correlation between the basal and non-basal like subgroup with the type of surgery, there was no statistical significance.

The dissemination of breast cancer is a common situation, because, from the time of diagnosis, about 5% of the patients present with distant conditions, according to the National Cancer Statistic Review[49]. The most common places of metastization are soft parts, bones, liver, and lungs[50]. In the metastatic phase, the disease always presents an unfavorable prognosis, with mean survival ranging from 24 and 42 months, and mean survival rate in 5 to 10 years. During the period of evaluation of our sample, all patients were followed-up and assessed in the follow-up of the presence or absence of distant metastasis. There was metastasis in 30 patients, which represented 24%, and absence in 95 patients (76%). In patients with metastasis, the bone type was more common, in 14 patients (46.6%), followed by lung and liver, with 5 patients for each, in a total of 10 patients (33.3%). In an interesting survey by Koo et al.[51], in 34 cases of metastatic cancer, the liver lesions, ER/PR+ and HER-2 were more prevalent; in brain metastasis, the overexpression of HER-2 was the most common one. In bone lesions, triple-negative tumors were prevalent. Bollen et al.[52] observed that patients with bone metastasis in the triple negative had mean survival of 6.7 months, unlike patients with positive receptors, whose survival was 22.5 months. In our survey, there was no correlation between the presence or absence of metastasis and the basal and non-basal like group.

Together with the classic parameters, like tumor size staging, axillary nodule and metastasis (TNM) and cell proliferation markers, other tumor markers have been used to predict tumor behavior, and the response to therapy in breast cancer. Among the markers verified by the immunohistochemical test, the most used in clinical practice are hormone receptors and HER-2[52]. The normal breast cell presents estrogen and progesterone receptors in their nuclei, detected through the immunohistochemical method. The level of receptors for steroid, estradiol (RE) and/or progesterone (PR) hormones in the tumor tissue constitutes strong indication of the level of hormone dependence in the mammary neoplasm[7]. Women with positive cancers for hormone receptors have prognosis slightly better than women with carcinomas that are negative to hormone receptors[53]. The evaluation of hormone receptors is more valuable to predict response to therapy, and hormone therapy usually has an excellent response in positive cases, with little or no response to this type of treatment in negative cases[54]. The overexpression of HER-2 is associated with poor prognosis, however, its evaluation has been mostly used to determine response to specific therapy. The triple-negative tumors represent about 15% of the total breast tumors, and affect younger patients more often, usually before menopause[55]. Vallegos et al.[48], in a survey including 1,524 patients, verified that approximately half of all cases were classified as positive ER/PR, and negative HER-2 (Luminal A subtype), corresponding to 49.3%; about 13.2% were identified as positive ER/PR/HER-2, and tumors in the triple-negative subtype (negative ER/PR/HER-2) were observed in 21.4% of the patients, demonstrating a very similar result to that found in our study. Wang et al.[46] found the triple-negative in 16.9% of the 835 patients with breast cancer, and these patients are more prone to developing distant metastasis.

In a recent review, Carter et al.[34] found prevalence of the high level of HER-2, between 0 and 38%, with mean of 18%, in women with breast cancer. In this study, we found 32% of positivity in the patients.

Our molecular biology techniques allow determining the true genetic signatures of the tumor by analyzing thousands of genes simultaneously. There is a new era of prognostic and predictive factors in the response to breast cancer treatment[54]. These tumors are classified in five subtypes: luminal A, luminal b, normal epithelium, basal-like and overexpression of HER-2[55,56]. We observed that tumors with good prognosis are luminal A and B and normal epithelium, whereas the evolution is worse in the basal-like and in the overexpression of HER-2 types. Even though there has not been a study about genetic signature in our analysis, we tried to conduct a classification of the groups based on the immunohistochemical criteria. There are studies that use immunohistochemistry in the subdivision of these genetic groups; however, further prospective, large studies are necessary to verify the correlation between these findings and genetic classification[57]. The genetic signature method has brought more independent prognostic information in relation to clinical-pathological prognostic factors[58,59].

After the immunohistochemical analysis of EGFR, cytokeratin CK5/6 and KI-67, we observed that these markers are associated with triple-negative breast carcinomas. This type of basal-like carcinoma is distinguished by the expression of keratins, which are more typical of myoepithelial cells. EGFR was overexpressed in 76 patients (97.4%), which is very characteristic in the basal-like subtype in triple-negatives, which was significant. Our results

also showed that triple-negative tumors have higher expression of the proliferation of KI-67 in the basal-like subtype, with 58.8%, than in the non-basal like subtype, with 30/6%, which is associated with worse prognosis in the evolution of the disease, normally presenting score higher than 15. In the statistical test, the KI-67 factor was significant, indicating that, in average, the value of this marker is different between the group of basal and non-basal like patients. Even with this prevalence in these groups, the independence test was significant only in factors CK5/6, EGFR and histological type, indicating that these factors are determinant for this subtype of the carcinoma. Kanapathy et al.[60] observed, in 340 patients diagnosed with breast cancer, that 12.4% (42) were triple-negative and were strongly associated with EGFR, CK5/6, and high level of KI-67 proliferation.

The patients who underwent neoadjuvant and adjuvant chemotherapy in triple-negative cancer, as well as radiotherapy, which was carried out at the location and on the supraclavicular fossa, from 25 to 30 sessions. Neoadjuvant chemotherapy was indicated in cases of locally advanced tumors. The anthracycline-taxane combination was chosen for 4 to 6 months, and, in this group, showed the best pathological complete response (PCR) in the breast and axilla, of 43.2%, for patients with negative hormone receptors. It has been consistently demonstrated that PCR is a very good prognostic factor for long-term benefits, especially for triple-negative patients[61,62], who, in general, reach 28 to 32%

rates of PCR[61]. The anthracycline-taxane combination should be, whenever possible, chosen due to the best rates of PCR[63,64]. There is experimental evidence that the addition of salts of platinum can be beneficial for triple-negatives, especially for patients with BRCA1 mutation[65,66].

Nowadays, the study of molecular biology, including the genetic signature, has been important to define the therapeutic sensitivity and to study small tumors better, free axilla, and considered, mostly, of good prognosis, may present with early recurrence; others, sometimes considered to be complicated, have favorable evolution. The evaluation of the triple-negative basal and non-basal like molecular subtype is very important to identify patients with worse prognosis. It is important not to base a diagnosis exclusively on the results of the immunohistochemical reactions. It is necessary to compare them with the histopathological findings and with the clinical data and imaging of the case.

CONCLUSIONS

The triple-negative basal and non-basal like tumors are different entities. In the three-year follow-up, the prognostic factors that mostly influenced the basal and non-basal like subtype were age, in young patients, histological type, and cytokeratin CK5/6, with higher significance level in factors EGFR and KI-67.

REFERENCES

1. Tavassoli FA. Normal development and anomalies of the breast. In: Pathology of the Breast; 2003. p. 45.

2. American Cancer Society. Leading sites of new cancer cases and deaths-2007 estimates [Internet]. 2007 [cited 2017 nov 22]. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/leading-sites-of-new-cancer-cases-and-deaths-2017-estimates.pdf

3. Page DL, Dupont WD. Anatomic markers of human premalignancy and risk of breast cancer. Cancer. 1990;66(Suppl 6):1326-35.

4. van't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature. 2002;415(6871):530-6. DOI: 10.1038/415530a

5. Page DL, Jensen RA, Simpson JF. Routinely available indicators of prognosis in breast cancer. Breast Cancer Res Treat. 1998;51(3):195-208.

6. Lakhani SR, Ellis, IO, Schnitt SJ, Tan PH, van de Vijver MJ. WHO classification of tumors of the breast. Lyon: IARC Press; 2012.

7. Reis-Filho JS, Westbury C, Pierga JY. The impact of expression profiling on prognostic and predictive testing in breast cancer. J Clin Pathol. 2006;59(3):225-31. DOI: 10.1136/jcp.2005.028324

8. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. America society of clinical oncology/college of america pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med. 2007;131(1):18-43. DOI: 10.1043/1543-2165(2007)131[18:ASOCCO]2.0.CO;2

9. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American society of clinical oncology/college of american pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med. 2010;134(7):e48-72. DOI: 10.1043/1543-2165-134.7.e48

10. American College of Radiology. Mammography. In: Illustrated breast imaging reporting and data system (BI-RADS). 4th ed. Reston: American College of Radiology; 2003.

11. Pascalicchio JC, Fristachi CE, Baracat FF. Câncer da mama: fatores de risco, prognósticos e preditivos. Rev Bras Mastol. 2001;11:71-84.

12. Colleoni M, Rotmensz N, Peruzzotti G, Maisonneuve P, Orlando L, Ghisini R, et al. Role of endocrine responsiveness and adjuvant therapy in very young women (bellow 35 year) with operable breast cancer and node negative disease. Ann Oncol. 2006;17(10):1497-503. DOI: 10.1093/annonc/mdl145

13. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol. 2009;20(8):1319-29. DOI: 10.1093/annonc/mdp322

14. Sales RA, Mcguire WL, Clark GM. Prognostic factors in breast cancer. Semin Surg Oncol. 1989;5(2):102-10.

15. Albain KS, Allred DC, Clark GM. Breast cancer outcome and predictors of outcome: are there age differentials? J Natl Cancer Inst Monogr. 1994;(16):35-42.

16. van Belle V, van Calster B, Brouckaert O, Bempt IV, Pintens S, Harvey V, et al. Qualitative assessment of the progesterone receptor and HER-2 improves the nottingham prognostic index up to 5 years after breast cancer diagnosis. J Clin Oncol. 2010;28(27):4129-34. DOI: 10.1200/JCO.2009.26.4200

17. Nixon AJ, Neuberg D, Hayes DF, Gelman R, Connolly JL, Schnitt S, et al. Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. J Clin Oncol. 1994;12(5);888-94. DOI: 10.1200/JCO.1994.12.5.888

18. Colonna M, Delafosse P, Uhry Z, Poncet F, Arveux P, Molinie F, et al. Is breast cancer incidence increasing among young women? An analysis of the trend in France for the period 1983-2002. Breast 2008;17(3):289-92. DOI: 10.1016/j.breast.2007.10.017

19. Sidoni A, Cavaliere A, Bellezza G, Scheibel M, Bucciarelli E. Breast cancer in young women: clinicopathological features and biological specificity. Breast. 2003;12(4):247-50.

20. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the Her-2/neu oncogene. Science. 1987;235(4785):177-82.

21. Dati C, Muraca R, Tazartes O, Antoniotti S, Perroteau I, Giai M, et al. C-erbB-2 and ras expression levels in breast cancer are correlated and show a co-operative association with unfavorable clinical outcome. Int J Cancer. 1991;47(6):833-8.

22. Clark GM. Interpreting and integrating risk factors for patients with primary breast cancer. J Natl Cancer Inst Monogr. 2001:17-21.

23. Farzadnia M, Meibodi NT, Shandiz Fh, Mahmoudi M, Bahar M, Memar B, et al. Evaluation of HER2/neu oncoprotein in serum and tissue samples of women with breast cancer: correlation with clinicopathological parameters. Breast. 2010;19(6):489-92. DOI: 10.1016/j.breast.2010.05.012

24. Newman LA, Mason J, Cote D, Vin.Y, Carolin K, Bouwman D, Colditz GA. African-American ethnicity, socioeconomic status, and breast cancer survival: a meta-analysis of 14 studies involving over 10,000 African-American and 40,000 White American patients with carcinoma of the breast. Cancer. 2002;94(11):2844-54. DOI: 10.1002/cncr.10575

25. Elledge RM, Clark GM, Chamness GC, Osborne CK. Tumor biologic factors and breast cancer prognosis among white, Hispanic, and black women in the United States. J Natl Cancer Inst. 1994;86(9):705-12

26. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K,. Race, breast cancer subtypes, and survival in the Carolina breast cancer study. JAMA. 2006;295(21):2492-502. DOI: 10.1001/jama.295.21.2492

27. Lund MJ, Trivers KF, Porter PL, Coates RJ, Leyland-Jones B, Brawley OW, et al. Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. Breast Cancer Res Treat. 2009;113(2):357-70. DOI: 10.1007/s10549-008-9926-3

28. Carvalho FM, Bacchi LM, Pincerato KM, Van de Rijn M, Bacchi CE. Geographic differences in the distribution of molecular subtypes of breast cancer in Brazil. BMC Womens Health. 2014;14:102. DOI: 10.1186/1472-6874-14-102

29. Tavassoli FA, Devilee P. Pathology and genetics of tumors of the breast and female genital organs. Lyon: WHO/IARC; 2003.

30. Simpson JF, Page DL. Prognostic value of histopathology in the breast. Semin Oncol. 1992;19(3):254-62.

31. Diab SG, Clark GM, Osborne CK, Libby A, Allred DC, Elledge RM. Tumor characteristics and clinical outcome of tubular and mucinous breast carcinomas. J Clin Oncol. 1999;17(5):1442-8. DOI: 10.1200/JCO.1999.17.5.1442

32. Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res. 2004;6(3):r149-56. DOI: 10.1186/bcr767

33. Tot T. The diffuse type of invasive lobular carcinoma of the breast: morphology and prognosis. Virchows Arch. 2003;443(6):718-24. DOI: 10.1007/s00428-003-0881-4

34. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer. 1989;63(1):181-7.

35. Uemura G, Luca L, Rodrigues JR, Vespoli HM, Carvalho LR, Traiman P. Um estudo da expressão de marcadores imunohistoquímico e fatores anatomoclínicos de câncer de mama em pacientes axila negativas. Rev Bras Mast. 2003;3(3):127-32

36. Fischer B, Slack NH, Bross ID. Cancer of the breast: size neoplasm and prognosis. Cancer. 1969;24(5):1071-80.

37. Mattes MD, Bhatia JK, Metzger D, Ashamalia H, Katsoulakis E. Breast cancer subtype as a predictor of lymph node metastasis according to the SEER registry. J Breast Cancer. 2015;18(2):143-8. DOI: 10.4048/jbc 2015.18.2143

38. Bacha OM, Zettler CG, Gonzales F, Grossmann S. Associação do c-erbB-2 com linfonodos axilares e outros fatores prognósticos no câncer de mama. Rev Bras Oncol. 2004;1(3):31-4

39. Yuan P, Xu BH, Zhang C, QI J. Serum her-2/neu level and related factors in patients with breast cancer. Chinese J Oncology. 2003;25(6):573-4.

40. Imoto S, Kitoh T, Hasebe T. Serum c-erB-2 levels in monitoring of operable breast cancer patients. Jpn J Clin Oncol. 1999;29(7):336-9

41. Ricci MD, Junqueira PA. Marcadores moleculares em câncer de mama preditivos de metástases axiliares. Rev Assoc Med Bras. 2008;54(3):189. DOI: 10.1590/S0104-42302008000300001

42. Veronesi U, Galimberti V, Zurrida S, Merson M, Greco M, Luini A. Prognostic significance of number and level of axillary node metastases in breast cancer. Breast. 1993;2(4):224-8. DOI: 10.1016/0960-9776(93)90004-Y

43. Viale G, Maiorano E, Pruneri G, Mastropasqua MG, Valentini S, Galimberti V, et al. Predicting the risk for additional axillary metastases in patients with breast carcinoma and positive sentinel lymph node biopsy. Ann Surg. 2005;241(2):319-25

44. Giuliano AE. Intradermal blue dye to identify sentinel lymph node in breast cancer. Lancet. 1997;350(9082):958. DOI: 10.1016/S0140-6736(05)63297-7

45. Cancello G, Maisonneuve P, Rotmensz N, Viale G, Mastropasqua MG, Pruneri G, et al. Prognosis and adjuvant treatment effects in selected breast cancer subtypes of very young women (<35 years) with operable breast cancer. Ann Oncol. 2010;21(10):1974-81. DOI: 10.1093/annonc/mdq072

46. Wang SL, Li YX, Song YW, Wang WH, Jin J, Liu YP, et al. Triple-negative or Her-2 positive status predicts higher rates of locoregional recurrence in node-positive breast cancer patients after mastectomy. Int J Radiat Oncol Biol Phys. 2011;80(4):1095-101. DOI: 10.1016/j.ijrobp.2010.03.038

47. Curigliano G, Viale G, Bagnardi U, Fumagalli L, Locatelli M, Rotmensz N, et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node negative breast cancer. J Clin Oncol. 2009;27(34):5693-9. DOI: 10.1200/JCO.2009.22.0962

48. Vallejos CS, Gomez HL, Cruz WR, Pinto JA, Dyer RR, Velarde R, et al. Breast cancer classification according to immunohistochemistry markers: subtypes and association with clinicopathologic variables in a peruvian hospital database. Clin Breast Cancer. 2010;10(4):294-300. DOI: 10.3816/CBC.2010.n.038

49. National Cancer Statistic Review: 1973-1989. NIH Pub.No.92-2789. NCI Bethesda; 1992.

50. Valagussa P, Bonadonna G, Veronesi U. Patterns of relapse and survival following radical mastectomy. Analysis of 716 consecutive patients. Cancer. 1978;41(3):1170-8.

51. Koo JS, Jung W, Jeong J. Metastatic breast cancer shows different immunohistochemical phenotype according to metastatic site. Tumori. 2010;96(3):424-32.

52. Bollen L, Wibmer C, Wang M, Van der Linden YM, Leithner A, Bünger CE, et al. Molecular phenotype is associated with survival in breast cancer patients with spinal bone metastases. Clin Exp Metastasis. 2015;32(1):1-5. DOI: 10.1007/s10585-014-9685-y

53. Moriya T, Kozuka Y, Kanomata N, Tse GM, Tan PH. The role of immunohistochemistry in the differential diagnosis of breast lesions. Pathology. 2009;41(1):68-76. DOI: 10.1080/00313020802563544

54. Gaforio JJ, Serrano MJ, Sanchez-Rovira P, Sirvent A, Delgado-Rodriguez M, Campos M, et al. Detection of breast cancer cells in the peripheral blood is positively correlated with estrogen-receptor status and predicts for poor prognosis. Int J Cancer. 2003;107(6):984-90. DOI: 10.1002/ijc.11479

55. Anderson WF, Chatterjee N, Ershler WB, Brawley OW. Estrogen receptor breast cancer phenotypes in the surveillance, epidemiology, and end results database. Breast Cancer Res Treat. 2002;76(1):27-36.

56. Bacchi LM, Corpa M, Bacchi CE, Carvalho FM. Caracterização anatamopatológica e imunofenotípica de carcinomas de mama em mulheres jovens. Rev Bras Mastol. 2009;19(2):42-6.

57. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747-52. DOI: 10.1038/35021093

58. Edén P, Ritz C, Rose C, Fernö M, Peterson C. Good Old clinical markers have similar power in breast cancer prognosis as microarray gene expression profilers. Eur J Cancer. 2004; 40(12):1837-41. DOI: 10.1016/j.ejca.2004.02.025

59. Dowsett M, Cooke T, Ellis I, Gullick WJ, Gusterson B, Mallon E, Walker R. Assessment of HER2 status in breast cancer: why, when and how? Eur J Cancer. 2000;36(2):170-6.

60. Kanapathy Pillai SK, Tay A, Nair S, Leong CO. Triple negative breast cancer is associated with EGFR, CK5/6 and c-KIT expression in Malaysian women. BMC Clin Pathol. 2012;12:18. DOI: 10.1186/14726890-12-18

61. Fisher ER, Sass R, Fischer B. Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol 04). Cancer. 1984;53:712-23.

62. Fisher B, Bauer M, Wickerham DL, Redmond CK, Fisher ER, Cruz AB, et al. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. Cancer. 1983;52(9):1551-7.

63. Clark GM. Prognostic and predictive factors in: diseases of the breast (Harris JR) Philadelphia. Lippincott. 2010:461-8.

64. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012;30(15):1796-1804. DOI: 10.1200/JCO.2011.38.8595

65. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol. 2008;26(8):1275-1281. DOI: 10.1200/JCO.2007.14.4147

66. Von Minckwitz G, Kümmel S, Vogel P, Hanusch C, Eidtmann H, Hilfrrich J, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst. 2008;100(8):552-62. DOI: 10.1093/jnci/djn089

THE IMPACT OF SENSORY ALTERATIONS ON UPPER LIMB FUNCTION AFTER A MASTECTOMY

Impacto das alterações sensitivas pós-mastectomia na funcionalidade do membro superior

Lidiane Régia Pereira Braga de Britto[1]*, Emanoella Carneiro de Souza[1], Lucimila Teixeira Ribeiro[1], Paulo Adriano Schwingel[1], Auxiliadora Renê Amaral de Melo[1], Paulo Loivo do Nascimento[2], Gray Josland Simões Portela[2]

ABSTRACT

Objective: To perform a descriptive analysis of the physical and clinical profile of women after a mastectomy, as well as to verify the functionality of the ipsilateral upper limb after surgery and to evaluate which quality of life questionnaire domains have repercussions on the functional capacity of this part of the body. **Methods:** Cross-sectional descriptive study, performed at the Centro de Oncologia Dr. Muccini, in Petrolina (Pernambuco, Brazil), with the participation of 53 patients. We used the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire to evaluate the functionality of the ipsilateral upper limb after surgery, and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and its breast cancer specific module (EORTC-QLQ-BR23) to measure quality of life. **Results:** The symptoms had a significant impact on the function of the patients' upper limbs. Statistically significant correlations (p<0.05) were observed between the total DASH score and the symptoms (r=0.451 in the QLQ-C30 and r=0.535 in the QLQ-BR23) and the functionality (r=-0.488 and r=-0.448), which were negative. There was also a statistically significant association (p=0.001) between limitation in activities of daily living (ADLs) and the subjective presence of lymphedema. **Conclusion:** The sensory alterations resulting from a mastectomy are the main factors responsible for the development of modifications that affect the functionality of the ipsilateral upper limb after surgery. The subjective sensation of lymphedema was associated with limitations in the ADLs and with a decrease in the arm's functional capacity.

KEYWORDS: Breast neoplasms; quality of life; upper extremity; sensation; mastectomy.

RESUMO

Objetivo: Realizar a análise descritiva do perfil físico e clínico de mulheres após mastectomia, além de verificar a funcionalidade do membro superior homolateral à cirurgia e avaliar quais os domínios do questionário de qualidade de vida têm repercussões na capacidade funcional desse segmento corporal. **Métodos:** Estudo descritivo de corte transversal, realizado no Centro de Oncologia Dr. Muccini, em Petrolina (PE), com a participação de 53 pacientes. A funcionalidade do membro superior homolateral à cirurgia foi mensurada por meio do questionário *Disability of the Arm, Shoulder and Hand* (DASH) e a qualidade de vida por meio do *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire* (EORTC-QLQ-C30) e seu módulo específico para câncer de mama (EORTC-QLQ-BR23). **Resultados:** A sintomatologia teve impacto importante na função dos membros superiores das pacientes, uma vez que foram verificadas correlações estatisticamente significativas (p<0,05) entre o escore total do DASH com a sintomatologia (r=0,451 no QLQ-C30 e r=0,535 no QLQ-BR23) e a funcionalidade (r=-0,488 e r=-0,448), sendo estas negativas. Foi também verificada associação estatisticamente significante (p=0,001) entre limitação nas atividades da vida diária (AVDs) e presença subjetiva de linfedema. **Conclusão:** As alterações sensitivas decorrentes da mastectomia são as principais responsáveis pelo desenvolvimento de modificações que afetam a funcionalidade do membro superior homolateral à cirurgia. A sensação subjetiva de linfedema teve associação com limitações nas AVDs e redução da capacidade funcional do braço.

PALAVRAS-CHAVE: Neoplasias da mama; qualidade de vida; extremidade superior; sensação; mastectomia.

INTRODUCTION

Breast cancer is the most common type of malignant neoplasm in Brazil's female population. In 2016, estimates reported 57,960 new cases, of which 11,190 occurred in the Northeast, and of which 2,550 were in Pernambuco. The death rates are still high when compared with those from developed countries, with 14 deaths for every 100 thousand women[1].

This situation may be attributed to the fact that the disease is diagnosed in advanced clinical stages (stages III and IV), which causes a worse prognosis and a lower survival rate due to the need for a more aggressive treatment[2]. The practices for tumor management depend on several factors, such as tumor staging, lesion size, and tumor histopathological heterogeneity[3].

Therefore, a total or conservative mastectomy associated with axillary lymphadenectomy has been the standard surgical treatment in conjunction with other alternatives, such as chemotherapy, radiotherapy, and hormone therapy. However, this procedure may cause severe morbidity in the ipsilateral upper limb, especially when associated with postoperative radiotherapy[4,5].

The morbidities presented during or after treatment include complications like lymphedema, sensory alterations, a decrease in muscle strength, and a reduction in movement amplitude (ADM) and of the functional capacity of the upper limb involved. These recurring complaints are mostly reported by women after a mastectomy and they are also indicated as implications due to the higher complexity of this treatment, considering they interfere in the patients' quality of life (QoL) and functionality[6,7].

As such, it is important to know the repercussions of the surgical treatment with an emphasis on these two aspects. Considering that QoL is an important prognosis factor for survival[8,9], the functional capacity constituted of motor, sensorial and cognitive skills, is directly associated with the possibility of performing activities of daily living (ADLs) in a dependent manner. Thus, functional capacity alterations may cause some disabling[10].

Therefore, due to the relevance for both health professionals and for patients, this study aimed to perform a descriptive analysis of the clinical and physical profile of the women being evaluated, as well as to verify the functionality of the ipsilateral upper and to assess which domains of the QoL questionnaire have repercussions on the functional capacity of this body part.

METHODS

This is a descriptive study with a cross-sectional approach that was carried out at the Centro de Oncologia Dr. Muccini (CEONCO) in Petrolina (Pernambuco, Brazil) with women who underwent a mastectomy as treatment for breast cancer. The CEONCO is a center of oncologic specialties of public service through the Brazilian Public Health System (Sistema Único de Saúde-SUS) and philanthropy, under the direction of the Maternity and Child Support Association (Associação de Amparo à Maternidade e à Infância- APAMI).

Fifty-three patients were analyzed in this article. The inclusion criteria were that they should have performed a unilateral mastectomy and should be doing regular check-ups at CEONCO. Before the questionnaires were used, all subjects received explanations on the purpose of the research and about the Free Informed Consent (TCLE) form. Patients who had any previous orthopedic dysfunction (bursitis, impact syndrome), cognitive deficits that prevented them from understanding the study, the presence of another type of malignant tumor, and those who did not sign and/or did not agree with the TCLE, were excluded from the study.

Collection was performed between August 2015 and April 2016. Personal, socioeconomic and clinical-surgical data were obtained through electronic records. This analysis done beforehand enabled access to the day when the patient would have a medical appointment and, thus, could be informed on the research and the use of the questionnaires.

To assess the functionality of the ipsilateral upper limb after surgery, we used the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, which was validated in Portuguese by Orfale et al.[11]. This tool is comprised of 30 self-applicable questions and two optional modules: one for sports and music activities and another for work. The items are related to the intensity of the symptoms of pain, weakness, stiffness and paresthesia of the upper limb. They also quantify the level of difficulty to perform ADLs, the ability to participate in social activities, difficulty in sleeping and the psychological affects that limb alterations cause to the patient. The questionnaire uses as reference the week before the use of the instrument, and its score varies from 0 to 100. The higher the score, the lower the upper limb functionality[11]. It is noteworthy that the optional modules were not used in this research.

QoL was verified through the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), version 3.0, and its specific module for breast cancer (Breast Cancer Module [EORTC-QLQ-BR23]). The EORTC-QLQ-C30 is comprised of 30 items, which are divided into: 5 functional scales (physical, role/performance, cognitive, emotional, and social); 3 symptoms (fatigue, pain and nausea/vomiting); and 6 simple items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties). The EORTC-QLQ-BR23 specific questionnaire includes 23 questions, which are distributed into function and symptoms scales. The scores vary from 0 to 100. For the function scales, the higher score the better the QoL. For the symptom scales, the higher the score the worse the QoL. As recommended, both questionnaires were applied by means of interviews[12].

In the statistical analysis, the data were gathered through double typing performed using Microsoft Excel® (Microsoft Corporation, Redmond, WA, United States). The data were then

processed and analyzed through the Statistical Package for the Social Sciences for Windows, version 20.0 (SPSS Inc., Chicago, IL, United States). The Kolmogorov-Smirnov test was used to verify the normality of the data. The homogeneity was determined by means of a histogram. Data were presented through descriptive statistics with categorical variables presented as absolute and relative frequencies. Continuous variables were represented by the central tendency and dispersion measurements. The correlation level between the variables was established using Pearson's linear correlation coefficient. The chi-square test was used to verify the associations between the DASH result, which was categorized by the subjective presence of lymphedema and with limitations in ADLs. A 5% significance level was adopted for all tests.

The Research Ethics Committee from the Universidade de Pernambuco (CEP-UPE) approved this project according to Resolution n. 510 of April 7th, 2016, from the Brazilian National Council of Health, which determines the standards and guidelines for the performance of research involving human beings (CAAE: 46228115.8.0000.5207).

RESULTS

Fifty-three women with an average age of 54.2 years old were included in the research. Data on the descriptive analysis of their socioeconomic profiles are found in Table 1. Among the participants, 34% were single and 39.6% did unpaid domestic activities. With regard to educational level, 24.5% of them were illiterate.

Concerning the physical-clinical profile of the participants, which is showed in Table 2, there was a higher prevalence of diagnoses in clinical staging IIA (28.3%). Considering the types of surgeries adopted, 54.8% women underwent surgeries with an axillary lymphadenectomy approach. Of the total patients, 47.2% had lymphedema and only 1 underwent breast reconstruction. When questioned about the limitations in ADLs, most of them reported some change. In addition, the mastectomy was performed within 5 years or less in 94.3% of the patients, and the mean time since the surgery was 2.8 years. Regarding the therapeutic modalities for breast cancer treatment, almost all of the patients underwent chemotherapy (92.5%), radiotherapy (88.7%), and hormone therapy (98.1%) treatments.

As to the overall assessment of upper limb functionality, the total mean exposed by the DASH was 25.52. When categorized, 79.2% (n=42) obtained a score lower than 50 and 20.8% (n=11) achieved a higher score than 50. Therefore, most of the study participants did not present severe damage to the ipsilateral limb's functions after surgery. However, there has been a statistically significant association between limitation in ADLs and subjective presence of lymphedema (p=0.001), in addition to a tendency of association between the subjective presence of lymphedema with categorized DASH (p=0.08).

In this sample, the symptoms had a significant impact on the function of the patients' upper limbs. The linear correlation between the DASH total score and the symptoms was positive and statistically significant (p<0.001), which shows that the higher the result of the last variable, the higher the difficulties in function in the segments that are measured both by the EORTC-QLQ-C30 (r=0.451) and by the EORTC-QLQ-BR23 (r=0.535). Only overall health condition did not present a linear correlation with the total DASH score (Table 3).

DISCUSSION

Regarding the socioeconomic profile of the patients included in the study, there were mostly single women aged between 50 to 60 years old that performed unpaid activities. This result is in agreement with data found in other studies carried out around the country[9,10,13], in which most of the analyzed population was older than 50 years old (61.0%), was married or in a stable union (48.6%) and performed household chores as their main activity (60.0%)[9].

Table 1. Descriptive analysis of the women's socioeconomic profile.

Variable	n	%
Age (years old)		
<50	24	45.3
>50	29	54.7
Time since surgery (years)		
<5	50	94.3
>5	3	5.7
Marital status		
Married	21	39.6
Single	18	34.0
Divorced	8	15.1
Widowed	6	11.3
Educational level		
Illiterate	13	24.5
Incomplete elementary school	16	30.2
Complete elementary school	2	3.8
Complete high school	16	30.2
Complete upper school	6	11.3
Occupation		
Unpaid house activities	21	39.6
Farmer	9	16.9
Autonomous	10	18.9
Teacher	3	5.7
Retired	10	18.9

The education level was lower than the one found in other studies, in which 32.4% of the involved subjects had completed high school[9] and 79.4% had more than 8 years of study[13]. This fact may be attributed to the characteristics of the Northeastern Brazilian population, especially in the countryside, where a great number of people with the same age as the participants in this study did not have access to school or needed to drop out for some reason. In the National Household Survey carried out by the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*—IBGE) in 2014, around 16.6% of Northeastern Brazilians aged older than 15 years old declared themselves as illiterate and represented the highest rate of functional illiteracy in the country (27.1%)[13].

Regarding the clinical staging at diagnosis, most of the women were in the beginning stages of the disease (I, IIA and IIB). Sousa et al.[9] also obtained similar results. They reported the occurrence of 19, 25 and 20% of the diagnoses in stages I, IIA and IIB, respectively. Regarding the surgical approaches performed on patients in this study, 37.7% were quadrantectomies associated with axillary lymphadenectomy. This was also observed in the research of Fangel et al.[10]. The prevalence of conservative surgery was 77%, and 23% were radical mastectomies

Although patients who underwent immediate breast reconstruction had better scores on the QoL assessments[14] (this factor gives the mastectomized woman some physical, psychological and social[15] benefits), this procedure was performed on only one of the participants of the sample. Its practice is still not very common in public health services in countries of low and middle income[16].

The practices for breast cancer treatment, especially surgery and radiotherapy[5], cause physical and functional dysfunctions, such as alterations in upper limb functionality, considering that radiotherapy may influence the patients' appearance and the persistence of pain, causing chronic conditions that directly affect QoL[5,17,18]. Nevertheless, these data were not similar to the present research, considering that there was not a positive correlation between QoL and arm functionality.

Table 2. Descriptive analysis of the physical and clinical profile.

Variable	n	%
Diagnostic staging		
I	13	24.5
IIA	15	28.3
IIB	11	20.8
IIIA	7	13.2
IIIB	7	13.2
Type of surgery and axillary approach		
Modified radical mastectomy + BLS	12	22.6
Modified radical mastectomy + LA	9	17.1
Quadrantectomy + BLS	12	22.6
Quadrantectomy + LA	20	37.7
Lymphedema subjective perception*		
Yes	25	47.2
No	28	52.8
Perception of limitation in activities of daily living**		
Yes	34	64.2
No	19	35.8
Dominant hand		
Left	6	11.3
Right	47	88.7
The dominant hand is ipsilateral to the breast undergoing surgery		
Yes	23	43.4
No	30	56.6
Breast reconstruction		
Yes	1	1.9
No	52	98.1
Adjuvant chemotherapy		
Yes	49	92.5
No	4	7.5
Adjuvant radiotherapy		
Yes	47	88.7
No	6	11.3
Adjuvant hormone therapy		
Yes	52	98.1
No	1	1.9

BLS: sentinel lymph node biopsy; LA: axillary lymphadenectomy; *Reported feeling a heavy arm, tight clothes, a decrease in flexibility and stretched skin from the ipsilateral limb; **Reported difficulties in performing tasks previously done before the surgery.

Table 3. Correlation between the Disabilities of the Arm, Shoulder and Hand (DASH) and the domains of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and its specific module for breast cancer (EORTC-QLQ-BR23).

Variables	DASH	
	r-value	p-value
QLQ-C30 Domains		
Functionality	-0.488	0.001*
Symptoms	0.451	0.001*
Overall health condition	-0.111	0.428
QLQ-BR23 Domains		
Functionality	-0.448	0.001*
Symptoms	0.535	<0.001*

*Significant correlation to the 5% confidential limit.

Nevertheless, 47.2% of the women reported symptoms of lymphedema and 64.2% presented limitations in the ADLs. The main symptoms of lymphedema include pain, weight, stiffness and ADM decrease, which worsens daily function and negatively affects motor skills, causing negative impacts on labor, domestic and personal care function, as well as on recreational and social activities[6,8,19].

The incidence of arm lymphedema seems to increase over time, for at least 24 months after the diagnosis of breast cancer or after surgery. It is noteworthy that 94.3% of the women studied herein had had their mastectomy within 5 years[6]. This high rate of complication is around four times more probable when the surgical procedure is associated with axillary lymphadenectomy[6,19].

The results from the present study demonstrate that the higher the alterations in the symptoms of the patients analyzed through the QoL questionnaire, the worse the alterations in the functionality of the ipsilateral upper limb after surgery. This might occur due to the type of axillary approach performed in 54.8% of the participating women. Besides causing pain and reducing mobility in the upper limber after the mastectomy, the axillary lymphadenectomy is most responsible for these sensory alterations[19-21].

The lesion from the intercostobrachial sensory nerve results in frequent complaints of sensory alteration in the medial and posterosuperior region of the arm and axilla. The occurrence of sensory alteration in the upper limb exposes the patient to serious risks of injury that may favor infectious or inflammatory processes, causing a negative impact on functional capacity and QoL[20,21].

The study performed had some limitations regarding the reduced size of the sample. Furthermore, the investigated population is from a specific region in the countryside of Pernambuco state and a great number of them undergo treatment in other centers, with more complex services.

CONCLUSION

It was inferred that, in this sample, the sensory alterations due to surgical treatment for breast cancer are the main causes responsible for affecting the functionality of the ipsilateral upper limb. It was also found that the subjective sensation of lymphedema was associated with limitations in ADLs and with reduction of the arm's functional capacity.

REFERENCES

1. Brasil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Estimativa 2016: incidência de câncer no Brasil. Rio de Janeiro: INCA; 2015.

2. Gonçalves LLC, Santos SB, Marinho EC, Almeida AM, Santos AHS, Barros AMMS, et al. Câncer de mama feminino: aspectos clínicos e patológicos dos casos cadastrados de 2005 a 2008 num serviço público de oncologia de Sergipe. Rev Bras Saúde Matern Infant. 2012;12(1):47-54.

3. Costa MADL da, Chagas SRP. Quimioterapia neoadjuvante no câncer de mama operável: revisão da literatura. Rev Bras Cancerol. 2013;59(2):261-9.

4. Hayes SC, Johansson K, Stout NL, Prosnitz R, Armer JM, Gabram S, et al. Upper-body morbidity after breast cancer: incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. Cancer. 2012;118(8):2237-49.

5. Bezerra TS, Rett MT, Mendonça ACR, Santos de, Prado VM, DeSantana JM. Hipoestesia, dor e incapacidade no membro superior após radioterapia adjuvante no tratamento para câncer de mama. São Paulo. Rev Dor. 2012;13(4):320-6.

6. Disipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013;14:500-15.

7. Nascimento SL do, Oliveira RR de, Oliveira MMF de, Amaral MTP do. Complicações e condutas fisioterapêuticas após cirurgia por câncer de mama: estudo retrospectivo. Fisioter Pesq. 2012;19(3):248-55.

8. Majewski JM, Lopes ADF, Davoglio T, Leite JCC. Qualidade de vida em mulheres submetidas à mastectomia comparada com aquelas que se submeteram à cirurgia conservadora: uma revisão de literatura. Ciên Saúde Coletiva. 2012;17(3):707-16.

9. Sousa E, Carvalho FN de, Bergmann A, Fabro EAN, Dias R de A, Koifman RJ. Funcionalidade de membro superior em mulheres submetidas ao tratamento do câncer de mama. Rev Bras Cancerol. 2013;59(3):409-17.

10. Fangel LMV, Panobianco MS, Kebbe LM, Almeida AM de, Gozzo T de O. Qualidade de vida e desempenho de atividades cotidianas após tratamento das neoplasias mamárias. Acta Paul Enferm. 2013;26(1):93-100.

11. Orfale AG, Araújo PMP, Ferraz MB, Natour J. Translation into Brazilian Portuguese, cultural adaptation and evaluation of the reliability of the disabilities of the arm, shoulder and hand questionnaire. Braz J MedBiol Res. 2005;38(2):293-302.

12. Michels FA, Latorre MR, Maciel MS. Validity, reliability and understanding of the EORTC-C30 and EORTC-BR23, quality of life questionnaires specific for breast cancer. Rev Bras Epidemiol. 2013;16(2):352-63.

13. Brasil. Ministério do Planejamento, Orçamento e Gestão. Instituto Brasileiro de Geografia e Estatística (IBGE). Pesquisa Nacional por Amostra de Domicílios: Síntese de indicadores 2014. Rio de Janeiro, 2015. p.42-4.

13. Rett MT, Santos AKG dos, Mendonça CRA, Oliveira IA de, DeSantana JM. Physical therapy effects on upper functional performance after breast cancer surgery. Rev Ciên Saúde. 2013;6(1):18-24.

14. Oliveira RR de, Morais SS, Sarian LO. Efeitos da reconstrução mamária imediata sobre a qualidade de vida de mulheres mastectomizadas. Rev Bras Ginecol Obstet. 2010;32(12):602-8.

15. Paredes CG, Pessoa SG de P, Peixoto DTT, Amorim DN de, Araújo JS, Barreto PRA. Impacto da reconstrução mamária na qualidade de vida de pacientes mastectomizadas atendidas no Serviço de Cirurgia Plástica do Hospital Universitário Walter Cantídio. Rev Bras Cir Plást. 2013;28(1):100-4.

16. Sinaei F, Zendehdel K, Adili M, Ardestani A, Montazeri A, Mohagheghi MA. Association between breast reconstruction surgery and quality of life in Iranian breast cancer patients. Acta Med Iran. 2017;55(1):35-41.

17. Bezerra TS, Rett MT, Mendonça ACR. Santos de, Prado VM, DeSantana JM. Hipoestesia, dor e incapacidade no membro superior após radioterapia adjuvante no tratamento para câncer de mama. Rev Dor. 2012;13(4):320-6.

18. Reidunsdatter RJ, Rannestad T, Frengen J, Frykholm G, Lundgren S. Effects of contemporary breast radiation on health-related quality of life – Predictors of radiotherapy-related fatigue. Acta Oncol. 2011;50(8):1175-82.

19. Bregagnol RK, Dias AS. Alterações funcionais em mulheres submetidas à cirurgia de mama com linfadenectomia axilar total. Rev Bras Cancerol. 2010;56(1):25-33.

20. Santos MSM dos, Panobianco MS, Mamede MV, Meirelles MCCC, Barros VM. Sensibilidade tátil no membro superior de mulheres submetidas à linfonodectomia axilar por câncer de mama. Rev Bras Ginecol Obstet. 2009;31(7):361-6.

21. Venâncio L, Campanelli NC, Sousa L de. Sensibilidade em membro superior após cirurgia de câncer de mama com linfadenectomia. ConScientia Saúde. 2013;12(2):282-9.

EPIDEMIOLOGICAL PROFILE OF THE MASTOLOGY CLINIC IN A UNIVERSITY HOSPITAL IN THE NORTHWEST OF PARANÁ

Perfil epidemiológico do ambulatório de mastologia em um hospital universitário no noroeste do Paraná

Edgar Junji Ito[1]*, Antonio Soares Safar[1]

ABSTRACT

Introduction: With increased awareness about breast cancer, discovering a breast lump can cause emotional stress in patients. Thus, diagnostic methods are used to distinguish and confirm benign and malignant breast pathologies. **Objective:** To characterize the epidemiological profile of the Mastology Clinic of the University Hospital of Maringá, in a period of one year, defining the incidence of benign and malignant breast diseases in patients undergoing breast cancer screenings in the local public health network. **Methods:** A cross-sectional, retrospective and descriptive study, with data collection from patients seen at the Mastology Clinic from March 2015 to February 2016. **Results:** Of the 103 patients, 99% were female, 82.3% were between 40 and 69 years old, and 80.5% were white. Regarding the patient's main complaint, 55% had only one altered imaging exam, 7% had only clinical complaints, and 32% had a palpable nodule in addition to an altered imaging exam. The main findings in the imaging exams were nodules, present in 67.1% of mammograms and 80% of mammographic ultrasonography, with inconclusive or suspected classification in 77.9% of mammograms and 65.7% of ultrasonography. Biopsies were performed in 71.8% of the patients. Benign pathologies corresponded to 76.1% of the diagnoses and 25 cases of breast cancer were identified. **Conclusion:** The epidemiological profile of the Clinic presented similar characteristics to the literature during the period studied. Referrals to specialists were justified because the changes in the imaging exams warranted further investigation. Diagnostic procedures fulfilled their role, differentiating and confirming benign and malignant breast diseases.

KEYWORDS: Epidemiology; breast diseases; mammography; ultrasonography, mammary; mass screening; diagnosis.

RESUMO

Introdução: Com o aumento da conscientização sobre o câncer de mama, descobrir um nódulo mamário pode causar estresse emocional nos pacientes. Dessa forma, métodos diagnósticos são empregados para distinguir e confirmar patologias mamárias benignas e malignas. **Objetivo:** Caracterizar o perfil epidemiológico do Ambulatório de Mastologia do Hospital Universitário de Maringá, no período de um ano, definindo a incidência de patologias mamárias benignas e malignas em pacientes submetidos a rastreamento de câncer de mama na rede pública regional. **Método:** Estudo transversal, retrospectivo e descritivo, com a coleta de dados de pacientes atendidos no ambulatório de mastologia de março de 2015 a fevereiro de 2016. **Resultados:** Dos 103 pacientes, 99% eram mulheres, 82,3% entre 40 e 69 anos e 80,5% da cor branca. Em relação à queixa principal, 55% apresentaram exclusivamente um exame de imagem alterado, 7% apenas queixa clínica e 32% possuíam nódulo palpável além do exame de imagem com alterações. O principal achado nesses exames foram nódulos, presentes em 67,1% das mamografias e 80% das ultrassonografias mamárias, com classificação inconclusiva ou suspeita em 77,9% nas primeiras avaliações e 65,7% nas últimas. Biópsias foram realizadas em 71,8% dos pacientes. Patologias benignas corresponderam a 76,1% dos diagnósticos e 25 casos de câncer de mama foram identificados. **Conclusão:** O perfil epidemiológico encontrado no ambulatório analisado apresentou características semelhantes à literatura, no período estudado. Encaminhamentos para a especialidade apresentaram justificativa para tal pelas alterações nos exames de imagem que mereciam maior investigação. Procedimentos diagnósticos cumpriram seu papel, diferenciando e confirmando doenças mamárias benignas e malignas.

PALAVRAS-CHAVE: Epidemiologia; doenças mamárias; mamografia; ultrassonografia mamária; rastreamento; diagnóstico.

INTRODUCTION

Mastology is the medical specialty that studies breast diseases and has numerous connections with other areas (gynecology, pathology, genetics, radiology, oncology, surgery). Thus, modern mastologists need to blend several specific areas of knowledge in order to fully conduct their practice[1].

Discovering a palpable breast nodule or a nodule in a mammographic screening is an emotional factor that impacts most patients, in part due to people's increased access to information and breast cancer (CA) awareness campaigns[2]. In Brazil, in 2016, the National Cancer Institute (*Instituto Nacional do Câncer* – INCA) estimated 57,960 new cases of breast CA, with an estimated risk of 56.20 cases per 100 thousand women. Breast CA is the most frequent cancer among women in the south (74.30/100 thousand), southeast, mid-west and northeast regions, not considering non-melanoma skin tumors[3]. However, it should be noted that up to 80% of palpable breast tumors are benign and do not significantly increase the risk for developing breast CA[4]. Thus, benign breast diseases make up the vast majority of mammary complaints at routine gynecological visits. Gynecologists should not only refer patients to a mastologist, but also reassure them and treat their symptoms.

Although most breast diseases are benign, breast CA is distinguished by its high mortality rates and its locoregional and systemic therapy repercussions[1], due to surgeries such as mastectomies and chemotherapeutic and/or radiotherapeutic treatments. When current diagnosis methods, such as mammography (MMG), mammary ultrasonography (USG), needle cytology and biopsy, present suspicious and/or confirmatory results for breast CA, especially in patients with risk factors for the diseases (advanced age and family history, for example)[3], the survival rate for this disease is directly proportional to the tumor stage at the time of diagnosis[5]. This moment has a direct influence on the progression and prognosis of the disease, as the precocity of the diagnosis is directly proportional to the chances of cure[6].

Thus, in 2015, guidelines for the early detection of breast CA were developed by a work force coordinated by the INCA, which determined the necessity for a biennial mammography for women aged between 50 and 69 years old as recommended by the Brazilian Ministry of Health (MoH) for breast CA screening.[7] These recommendations are different from those from the Brazilian College of Radiology (*Colégio Brasileiro de Radiologia* – CBR), the Brazilian Mastology Society (*Sociedade Brasileira de Mastologia* – SBM) and the Brazilian Gynecology and Obstetrics Federation (*Federação Brasileira de Ginecologia e Obstetrícia* – FEBRASGO), which recommend an annual mammogram for all women between 40 and 69 years of age, for screening purposes[8].

The BI-RADS (Breast Imaging-Reporting and Data System) was used in order to classify mammary lesions identified in MMGs. In 1992, the American College of Radiology developed a system to standardize mammography reports. This system has been used in Brazil since 1998, according to the guidelines from CBR and FEBRASGO[9]. In order to monitor the quality of diagnostic imaging services performed by MMG, Ordinance No. 530, of the Ministry of Health, published in the Official Gazette of the Union (*Diário Oficial da União*) on March 27th, 2012, establishes the National Quality Mammography Program (*Programa Nacional de Qualidade em Mamografia* – PNQM)[10]. It is known that a poor-quality mammography may leave the patient mistakenly at ease and with a false sense of protection or, on the contrary, suggest an untrue breast lesion diagnosis that is under high suspicion for malignancy.

Hence there is an extreme importance to distinguish, accurately, benign breast diseases from malignant ones, through minimally invasive procedures and/or adequately reported mammograms, with the aid of both clinical epidemiological patients profiles. This can prevent iatrogenies, such as unnecessary surgical procedures or delayed breast CA diagnosis and its treatment.

The Mastology Outpatient Clinic of the *Hospital Universitário Regional de Maringá* (HUM) was recently set with the objective of evaluating cases of suspicious screening tests for breast CA in the public health system of the region. Patients are referred to this service so that the breast CA diagnosis may be investigated early on, and confirmed or discarded in an attempt to find solutions in the shortest time possible.

The general objective of this study was to characterize the epidemiological profile of the Mastology Outpatient Clinic of the HUM, from March 2015 to February 2016, specifically addressing the incidence of benign and malignant mammary pathologies and observing the BI-RADS classification of radiological findings in breast lesions.

METHODS

In order to meet the objectives proposed, a cross-sectional, retrospective and descriptive study was carried out. Data were collected based on the information found in medical chart records of patients seen at the Mastology Outpatient Clinic of the HUM, from March 2015 to February 2016.

The information obtained and subsequently analyzed included: gender, age, color/race, educational level, reason for referral to the outpatient clinic/main complaint, radiological tests (MMG and/or mammary USG) and respective BI-RADS classification, diagnostic procedure with fine needle aspiration (FNA), needle biopsy, core-biopsy (core-bx) or lesion/tumor excision, anatomopathological report/diagnosis/mammary pathology, family history of breast CA, and course of action.

The patients included in this study were found using the Hospital and Outpatient Management System (*Sistema de Gestão Hospitalar e Ambulatorial* – GSUS), and confirmed in the area of outpatient specialties clinics (mastology, in this case). The figures in the medical charts were recorded and, from them, a search in the Patient Record Service (*Serviço de Prontuário de Paciente* – SPP) of the HUM was performed.

The data were collected and stored in a table specifically made for the study, for further descriptive statistical analysis. Data such as the name of the patient, date of birth, parents, residence address, contact telephone numbers, National Health Card number, or any other information which would allow for the identification of patients were not included. Thus, an informed consent waiver was requested.

The purposes of this research were protocolized in the Commission for the Regulation of Academic Activities (*Comissão de Regulamentação de Atividades Acadêmicas* – COREA) of the HUM, submitted for consideration, and upon obtaining a favorable opinion under No. 103/2016, and in the Standing Committee on Ethics in Human Research (*Comitê Permanente de Ética em Pesquisa com Seres Humanos* – COPEP) of the *Universidade Estadual de Maringá* (UEM), were submitted for consideration under No. 1.788.120, and upon obtaining favorable opinion, were filed as CAAE 60403716.8.0000.0104.

RESULTS

After research in the GSUS system, 248 medical appointments were identified for the mastology outpatient clinic, from March 1st, 2015 to February 29th, 2016. Of those, 169 had their presence confirmed, 57 were missing, 11 were transferred and 11 were cancelled. Of the 169 confirmed appointments, 65 were from patients who had already been seen more than once within the period (meaning 65 outpatient return visits). Thus, the initial sample consisted of 104 patients who underwent mastology appointments in the mentioned period. Of the 104 medical charts in SPP, 1 was not found, therefore, the total number of reviewed charts was 103 patients.

The final sample consisted of 102 female patients and 1 single male patient. Age ranged from 12 to 74 years old, with a mean of 48 years of age, and 82.3% of the subjects were aged between 40 and 69 years old. Of the 103 patients, 80.5% were white/caucasian, 14.5% were light-skinned black people and 4.8% were dark-skinned black people. As for education, most of them (56.3%) had elementary school degrees (it was not specified whether the degrees were complete or incomplete), 6.7% were not literate, 29.1% had a high school degree and 7.7% had completed higher education. These data are displayed in Table 1.

Regarding the main complaint, 55% had only an altered imaging test as the reason for referral to the clinic, while 7% were referred there due to clinical complaints only (4% palpable nodule, 2% papillary discharge and 1% gynecomastia), without previous imaging tests. On the contrary, 32% of patients had a palpable nodule as a clinical complaint in addition to an altered imaging test. The remaining 6% included postoperative patients who had drainage of breast abscesses performed on them and were referred from the infirmary ward/emergency room for a follow-up.

With regard to the family history for breast CA, 74.7% of the subjects did not have any relatives with this diagnosis, while 16.5% had a positive family history for the condition (mother, sister, maternal aunt, maternal grandmother or unspecified degree of kinship); 8.7% were ignored because they didn't have this information on their charts.

Patients were already instructed to present, at their first visit, an imaging exam with alterations and their respective medical reports. Thus, 73 MMG and 70 mammary USG, performed in other places, were analyzed. The main variation in the imaging exams was mammary nodules, present in 67.1% of MMGs and 80% of USGs. Other findings may be observed in Table 2. As for

Table 1. The epidemiological profile of the patients regarding gender, age, race and education.

Characteristic	N	%	Characteristic	N	%
Gender			Race		
Female	102	99.0	White/Caucasian	83	80.5
Male	1	0.9	Light-skinned Black	15	14.5
Age (years)			Dark-skinned Black	5	4,8
<30	6	5.8	Education		
30 to 39	10	9.7	Illiterate	7	6.7
40 to 49	38	36.8	Elementary school	58	56.3
50 to 59	32	31.0	High School	30	29.1
60 to 69	15	14.5	College	8	7.7
≥70	2	1.9			

Table 2. Characteristics of the imaging exams evaluated in the first consultations with regard to the alterations found and the BI-RADS classification.

Mammography	N	%	Ultrasonography	N	%
Alterations			Alterations		
Absent	5	6.8	Absent	4	5.7
Nodules	49	67.1	Nodules	56	80.0
Benign calcifications	5	6.8	Cysts	11	15.7
Suspicious classifications	8	10.9	Heterogeneous area	1	1.4
Asymmetric density	6	8.2	Ductal dilation	1	1.4
Dense parenchyma	4	5.4	Signs of abscess	1	1.4
BI-RADS			BI-RADS		
0	32	43.8	0	0	0
1	5	6.8	1	4	5.7
2	6	8.2	2	7	10.0
3	5	6.8	3	13	18.5
4	20	27.3	4	42	60.0
5	5	6.8	5	4	5.7
6	0	0	6	0	0

the BI-RADS classification of these tests, 43.8% of MMGs were BI-RADS 0, 27.3% were BI-RADS 4 and 6.8% were BI-RADS 5. Regarding USGs, 60% were BI-RADS 4 and 5.7% were BI-RADS 5.

According to need and an adequate referral, new imaging exams were requested, and diagnostic procedures were performed. Thus, digital MMGs were performed in 24.2% of the patients, only a mammary USG was performed in 8.7%, a FNA (possibly USG-guided) in 33%, a core-bx (USG-guided or not, stereotaxic or not) in 38.8%, a nodulectomy/sectorectomy in 19.4% and there was a single case of prolactin dosage and nuclear magnetic resonance imaging (MRI) of the pituitary.

The main diagnosis found may be observed in Table 3. The diagnosis of "normal breast" was given to patients with MMG alterations (nodule or asymmetric density), which were not confirmed later in the mammary USG performed.

The final procedures (after the first consultation, diagnostic procedure and diagnostic conclusion) were outpatient discharge with a follow up in Basic Health Units (*Unidade Básica de Saúde* - UBS) (59.2%), a referral to a reference service (High-Complexity Oncology Centers — *Centros de Alta Complexidade em Oncologia*

– CACON) for oncologic treatment (25.2%), and a follow-up in the service itself (15.5%). Of the 25 patients with a breast CA diagnosis, 15 (60%) underwent the first visit, diagnostic procedures, a diagnostic conclusion with anatomopathological report, and a referral to a reference service in a period of 1 week. A total of 5 (20%) patients took 2 weeks to do so, and another 2 patients took 4 weeks. In another three cases, a longer time was taken— 50, 105 and 112 days. The mean time that the patient with breast CA remained in our service was 19.9 days, with a minimum of 7, a maximum of 112 and a median of 7 days.

DISCUSSION

Almost all of the patients were female (102 patients), except for a single male patient, aged 27 years old, with a complaint of gynecomastia and a positive family history of breast CA.

The age range was broad, covering youngsters, adults and elderly people, with 82.3% of the sample aged between 40 and 69 years old. The prevalence in this age range corroborates the fact of having greater attention to breast CA in the screening group, according to the recommendations, of 50 to 69 years of age from the MoH and 40 to 69 years of age from the SBM, FEBRASGO and CBR. Patients performing screening in primary health care, whether annually or biennially, who had alterations in their imaging exams and/or would require in-depth investigation, were referred to our outpatient clinic for such. Regarding race, the results found (80.5% White/Caucasian, 14.5% Light-skinned Black and 4.8% Dark-skinned Black) were compatible with the prevalence of those according to the 2010 Census of Maringá, published by the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* – IBGE) in 2011 (70.8% White/Caucasian, 21.9% Light-skinned Black and 0.03% Dark-skinned Black)[11], with some differences, considering that the population served in our outpatient clinic is not restricted to this municipality.

Since it is a specialized mastology outpatient clinic, the vast majority of patients (87.3%) referred to it already presented an imaging exam (MMG or mammary USG) at their first consultation. Palpable nodules was the main complaint, along with imaging exams, comprised 35.8% of the sample, and another 55.3% had only their altered imaging test as a main complaint, and denied any clinical symptoms in anamnesis. This probably reflects the attention given to breast CA screening, since 87.7% of patients with only an imaging exam as their main complaint were aged between 40 and 69 years old.

Family history of breast CA is an important risk factor for the onset of the disease, considering that gene alterations, such as the ones from the Breast Cancer Susceptibility Gene family (BRCA), increase the risk of developing it. It should be noted, however, that about nine of every ten breast CA cases occur among women with no family history[3]. Although this was not the study's objective, due to unreliable and/or ignored data (such as positive family

Table 3. Diagnoses of patients from the Mastology Outpatient Clinic of the HUM, from March 2015 to February 2016.

Diagnosis	N	%
Normal breast	4	3.6
Benign functional alterations of the breast	35	31.8
Benign nodule	21	60.0
Mammary cyst	9	25.7
Ductal ectasia	1	2.8
Not specified	4	11.4
Mastitis	7	6.3
Steatonecrosis	2	1.8
Eczema	1	0.9
Galactorrhea	1	0.9
Benign neoplasia	19	17.2
Fibroadenoma	11	57.8
Benign phyllodes tumor	3	15.7
Benign ductal papilloma	2	10.5
Simple adenosis	1	5.2
Angiolipoma	1	5.2
Gynecomastia	1	5.2
Benign microcalcifications	15	13.6
Atypical ductal hyperplasia	1	0.9
Breast CA	25	22.7
Ductal	22	88
Mixed	1	4
Not specified	2	8

history for first and/or second degree relatives, age at which the family member was diagnosed with breast CA, verified mutation in the BRCA1 or BRCA2 genes, and diagnosis of ovarian CA), it was not possible to perform an adequate analysis of hereditary risk of breast CA. In any case, it may be stated that, from the groups with negative (77 patients), positive (17) and ignored (9) family history, 18 (23.3%), 3 (17.6%) and 4 patients, respectively, were diagnosed with this disease.

In total, 73 MMGs and 70 mammary USGs were evaluated during first visits, whose main findings were nodules in 67.1 and 80% of them, respectively. There were also alterations identified as microcalcifications and/or MMG asymmetric densities and cysts and/or heterogeneous areas in the USGs. The majority of patients had a BI-RADS classification of 0, 4 or 5, i.e., tests presenting inconclusive, suspicious or highly suspicious findings for malignancy, respectively. These deserved further investigations, comprised by 77.9% of MMGs and 65.7% of mammary USGs. Approximately 25% of the sample needed to perform a new MMG in the service.

As for the MMGs performed in other services, it is worth noting that 43.8% of them had BI-RADS 0, an inconclusive result requiring another exam to be done (either a USG or a new MMG with an enhancement or compression of the inconclusive image). Poor quality of the exam, an inadequate report, or an inappropriate exam request (for instance, a MMG for young women with dense breast parenchyma, which makes a good evaluation rather impossible) are possible reasons for these results. It should be noted that, of the 32 patients with BI-RADS 0, only 4 of them were aged less than 40 years old.

Although it was only expected to have referrals of imaging exams with BI-RADS 0, 4 or 5 to the mastology outpatient clinic, 15 patients had BI-RADS 1, 2 or 3 in their MMGs and USGs (negative, benign or probably benign findings, respectively) and, even then, they were referred to a specialist for a more satisfactory evaluation. After reevaluation and new tests, when necessary, all 15 cases were diagnosed as benign.

Regarding diagnostic procedures, 71.8% of the patients were submitted to minimally invasive procedures: FNA (33%) and core-bx (38.8%). Of the 34 FNA, 21 were suggestive of fibroadenoma, of which 13 opted for an expectant treatment, 7 underwent nodulectomy (all confirmed benign pathology) and 1 chose to continue the core-bx investigation, resulting in a breast CA diagnosis. As for the remaining 13 FNA, 5 were confirmed to have mammary cysts, 4 were compatible with mastitis and steatonecrosis, and the other 4 were referred to nodulectomy/sectorectomy (confirming 2 fibroadenomas, 1 angiolipoma and 1 benign Phyllodes tumor). Forty patients were submitted to a core-bx procedure. Twenty-four of them (60%) were diagnosed with breast CA with a biopsy, 1 had an inconclusive result (confirmed CA diagnosis after nodulectomy) and 1 was diagnosed with an atypical ductal hyperplasia (risk precursor lesion). The other 14 core-bx were diagnosed as benign.

Twenty patients underwent nodulectomy and/or sectorectomy surgeries. Fifteen of those performed FNA or core-bx previously, which was not necessary in the other 5 (3 cases of nodulectomy with post-surgical confirmation of fibroadenoma and 2 cases of sectorectomy with a previous diagnosis of chronic mastitis). Of the 15 who underwent minimally invasive procedures, only 1 core-bx presented an inconclusive anatomopathological result and was confirmed by a post-nodulectomy for mixed invasive CA. The other 14 patients were diagnosed with benign pathologies (8 fibroadenomas, 2 benign Phyllodes tumors, 2 benign ductal papillomas, 1 angiolipoma and 1 simple adenosis). A third case of a benign Phyllodes tumor, confirmed in core-bx, was referred for treatment at another service.

There was only one case of galactorrhea, in which other tests such as prolactin dosage and a pituitary MRI were requested. Galactorrhea from a pharmacological cause was the diagnostic conclusion.

Of the 110 diagnoses (considering some patients had more than one pathology, such as nodules and mammary cysts, for example), 76.1% of them corresponded to benign pathologies. Only one case of atypical ductal hyperplasia and 25 cases of breast CA were diagnosed, of which 88% were ductal, corroborating the literature found[12]. Patients with breast CA were aged between 34 and 70 years old. However, 92% of them were aged between 40 and 70 years old. The mean age observed was 54 years old, similar to patients from other Brazilian states and other countries[13]. 72% were White/Caucasian, 24% Light-skinned Black and 4% Dark-skinned Black. Only 3 of the 25 subjects had a positive family history.

Breast CA is a multifactorial type of cancer, involving biological-endocrine factors, reproductive life, behavior and lifestyle. Aging, factors related to the reproductive life of women (nulliparity, having the first child after 30 years of age), family history of breast CA, and high-density mammary tissue (the ratio between the mammary glandular tissue and the adipose one) are the best-known risk factors for the development of this condition. Furthermore, alcohol consumption, excess weight, sedentarism and exposure to ionizing radiation are also considered potential agents[3]. Since the objective of this study was not to outline the profile of the patients diagnosed with breast CA, certain risk factors were ignored in the research because much of the aforementioned data was not found in medical charts. Likewise, due to the lack of information in medical records, no data were collected regarding the stage of the breast CA at the time of its diagnosis.

Thus, the final procedures performed were outpatient's discharge with a follow-up in UBSs (59.2%), a referral to a reference service for oncologic treatment (25.2%) and continuity in the service itself (15.5%). This presented an outpatient resolution rate of 84.4%.

It is important to highlight the time patients with breast CA spent in our service, from the moment of their first consultation

to their referral to a reference center (CACON). Of the 25 patients diagnosed with breast CA:

- 15 (60%) underwent their first consultation, diagnostic procedure, diagnostic conclusion with anatomopathological report and referral to the reference service within 1 week;
- 5 (20%) patients took 2 weeks;
- and 2 other patients took 4 weeks.

This was due to a delay in the pathology service and/or to the lack of attendance of the patient for the result of the biopsy. In another three cases, the time was excessively long, though each of them had its particularities. One patient remained in this service for 50 days due to an inconclusive core-bx and was submitted to a nodulectomy. She therefore had to wait for the bureaucratic paperwork for the surgical procedure, having confirmed breast CA in the anatomopathological report of the piece. Another patient presented herself to the outpatient clinic shortly before the end of the year, in 2015, and its holiday season. She had previously undergone a nodulectomy with a diagnosis of benign pathology, and therefore her biopsy was postponed, prolonging her stay up to 105 days. A third patient was affected by a strike from HUM professionals in April and May 2015, which caused the biopsy to be carried out 3 months after her first visit. Two weeks later she was referred to a reference service and remained in our service for 112 days.

Thus, the mean time between the first consultation and the referral to CACON was 19.9 days with a median of 7 days. It should be noted that, if we disregarded the three outlier cases, the mean time would be 10.5 days.

The more efficient the service, the faster the patient is diagnosed and can begin their treatment. The country has advances in breast CA treatments, with Federal Law No. 12.732/2012 granting every patient with neoplasia the right to receive their first treatment within 60 days from the day of the diagnosis[14]. Despite that, the mean time for diagnostics and for the beginning the treatment of patients with palpable tumors exceeds 180 days in most of the country[15]. With this in mind, there was a great effort so that breast CA diagnoses could be given in the shortest possible time, and patients could be referred to a reference service as soon as possible.

Regarding the case of atypical ductal hyperplasia, although an open biopsy was advisable to confirm a diagnosis of malignant neoplasia, it was decided to refer the patient to a reference service, after 14 days in our service. We consider such a decision to be appropriate as it avoids the risk of delayed probable diagnosis of malignant neoplasia in the aforementioned case.

A limitation of the study includes the fact that any research involving medical chart review (in this case, physical/printed ones) may affect data collection due to factors such as scarcity of information, poor inclusion of information, poor completion of the form and illegible handwriting. The lack of a standardized medical chart by the Mastology Outpatient Clinic of the HUM, which began its activities in January 2014, resulted in great difficulty for data collection. Thus, in order to improve anamnesis and the search for information, a standardized chart was created and adjusted for the clinic's reality, in mid-2016. With this, future studies in the area are expected to be more complete and to have fewer obstacles in data collection, in addition to most certainly improving patient care.

CONCLUSION

The present study concluded that this Mastology Outpatient Clinic in the HUM presented similar epidemiological characteristics to the literature in the studied period. Considering that it was a specialized clinic, most referrals were in fact justified, with imaging tests worthy of further investigation. Minimally invasive procedures fulfilled their roles in confirming benign and malignant breast diseases diagnoses. There was success in analyzing patients with alterations in their screening exams for breast CA, and determining the presence of a malignant disease in the shortest time possible.

The present study is pioneering in this region, since this mastology outpatient clinic has recently started its activities. This work is expected to allow for and encourage further studies in this area.

REFERENCES

1. Nazário AC, Elias S, Facina G, Araujo Neto JT. Mastologia: condutas atuais. Barueri: Manole; 2016.

2. Nazário AC, Rego MF, Oliveira VM. Nódulos benignos da mama: uma revisão dos diagnósticos diferenciais e conduta. Rev Bras Ginecol Obstet. 2007;29(4):211-9. DOI: 10.1590/S0100-72032007000400008.

3. Brasil. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Estimativa 2016: incidência de câncer no Brasil. Rio de Janeiro: INCA; 2015.

4. Boff RA, Wisintainer F. Mastologia moderna: abordagem multidisciplinar. Caxias do Sul: Mesa Redonda; 2006.

5. Nicolaou PK, Padoin LV. O retrato das políticas públicas no tratamento do câncer de mama no Brasil. Rev Bras Mastologia. 2013;23(3):92-4. DOI: 10.5327/Z0104-8058201300030006

6. Kim DD, Araujo AL, Tsai A, Kojima FH, Takashima JS, Otsuka Junior LF, et al. Saber é prevenir: uma nova abordagem no combate ao câncer de mama. Cien Saude Colet. 2010;15(Suppl 1):1377-81. DOI: 10.1590/S1413-81232010000700047

7. Brasil. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Diretrizes para a detecção precoce do câncer de mama no Brasil. Rio de Janeiro: INCA; 2015.

8. Urban LA, Schaefer MB, Duarte DL, Santos RP, Maranhão NM, Kefalas AL, et al. Recomendações do colégio brasileiro de radiologia e diagnóstico por imagem, da sociedade brasileira de mastologia e da federação brasileira das associações de ginecologia e obstetrícia para rastreamento do câncer de mama por métodos de imagem. Rev Bras Mastologia. 2012;45(6):334-9. DOI: 10.1590/S0100-39842012000600009

9. Caetano S, Mottola Junior J, Finguerman F, Goldman SM, Szejnfeld J. Mammographic assessment of a geographically defined population at a mastology referral hospital in São Paulo Brazil. PLoS One. 2013;8(9): e74270. DOI:10.1371/journal.pone.0074270

10. Lisboa FC, Siqueira F, Viana SM, Rodrigues JF, Nunes TR. Análise crítica do diagnóstico, tratamento e seguimento de pacientes com câncer de mama acompanhadas em serviço de mastologia do Distrito Federal. Rev Bras Mastologia. 2014;24(2):36-41. DOI: 10.5327/Z201400020002RBM

11. IPARDES – Instituto Paranaense de Desenvolvimento Econômico e Social. Caderno estatístico, município de Maringá. dezembro de 2012.

12. Muradas RR, Velho MT, Riesgo IS, Brum AD, Rossi RM, Piovezan JM, et al. Clinical and mammographic profile of patients with breast cancer surgically treated. Rev Assoc Med Bras. 2015;61(3):220-6. DOI: 10.1590/1806-9282.61.03.22

13. Cavalcanti LP, Simões PS, Silva MR, Galdino PN. Assistência em mastologia em uma Unidade de Referência do Sistema Único de Saúde no Ceará, Brasil. Rev Bras Cancerologia. 2012;58(4):603-9.

14. Brasil. Presidência da República. Lei Federal nº 12.732, de 22 de novembro de 2012. Dispõe sobre o primeiro tratamento de paciente com neoplasia maligna comprovada e estabelece prazo para seu início [Internet]. 2012 [cited 2014 Jan 15]. Available from: http://www.planalto.gov.br/ccivil_03/_ato2011-2014/2012/lei/l12732.htm

15. Gebrim LH, Shida JY, Hegg R, Topis T, Mattar A. Avaliação do tempo de início do tratamento, estadiamento histopatológico e positividade dos biomarcadores (RE, RP, HER-2) em 3.566 pacientes tratadas pelo SUS no período de 2012 a 2014, no Hospital Pérola Byington. Rev Bras Mastologia. 2014;24(3):65-9. DOI: 10.5327/Z201400030002RBM

THE IMPACT OF PHYSICAL THERAPY ON THE QUALITY OF LIFE OF WOMEN AFTER BREAST CANCER SURGERY

A influência da fisioterapia na qualidade de vida de mulheres após o tratamento cirúrgico do câncer de mama

Felipe Bernardino Rezende Maués[1]*, Saul Rassy Carneiro[1], Thalita da Luz Costa[1],
Bárbara Begot de Freitas Rosa[1], Pricila de Jesus Oliveira[1], Marcela Fagundes[1], Laura Maria Tomazi Neves[1]

ABSTRACT

Objective: To evaluate the impact of physical therapy on the quality of life of patients after breast cancer surgery. **Methods:** We included 16 female patients who underwent breast cancer surgery in this clinical, longitudinal, prospective, and convenience sample study. The patients underwent a mastectomy or a quadrantectomy through an axillary approach and were evaluated before and after 20 sessions of physical therapy. Quality of life was assessed by the European Organization for Research and Quality of Life Questionnaire C-30 (EORTC QLQ C-30) and the Breast Cancer Module (EORTC QLQ BR-23) questionnaire. For the statistical analysis, we used the Shapiro-Wilk test to evaluate the distribution of quality of life data. The data from before and after physical therapy was compared through the Wilcoxon test. **Results:** After participating in physical therapy, there was a significant improvement in physical function (p=0.023), cognitive function (p=0.033), social function (p=0.013), pain (p=0.025), fatigue (p=0.001), financial difficulty (p=0.007), and body image (p<0.001). **Conclusion:** According to the data presented in this study, we suggest that a physiotherapeutic approach positively impacts the quality of life of patients after breast cancer surgery.

KEYWORDS: Breast Neoplasms; Medical Oncology; Quality of Life; Physical Therapy (Techniques); Women's Health.

RESUMO

Objetivo: Avaliar a influência da fisioterapia na qualidade de vida de pacientes após o tratamento cirúrgico do câncer de mama. **Metodologia:** Neste estudo clínico, longitudinal, prospectivo e de amostra por conveniência foram incluídas 16 pacientes que realizaram tratamento cirúrgico do câncer de mama, submetidas à mastectomia ou quadrantectomia, associada à abordagem axilar. Elas foram avaliadas antes e depois de 20 sessões de fisioterapia. A qualidade de vida foi examinada pelos questionários European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ C-30) e Breast Cancer Module (EORTC QLQ BR-23). Para análise estatística, foi utilizado o teste de Shapiro-Wilk, para avaliação da distribuição dos dados sobre a qualidade de vida, sendo estes comparados antes e depois da fisioterapia por meio do teste de Wilcoxon. **Resultados:** Após a intervenção fisioterapêutica, houve melhora significativa em relação à qualidade de vida na função física (p=0,023), função cognitiva (p=0,033), função social (p=0,013), dor (p=0,025), fadiga (p=0,001), dificuldade financeira (p=0,007) e imagem corporal (p<0,001). **Conclusão:** De acordo com os dados apresentados no estudo, pode-se sugerir que a abordagem fisioterapêutica influencia positivamente na qualidade de vida de pacientes após o tratamento cirúrgico do câncer de mama.

DESCRITORES: Neoplasias da Mama; Oncologia; Qualidade de Vida; Fisioterapia; Saúde da Mulher.

INTRODUCTION

Breast cancer is the type of cancer that most affects women around the world. In Brazil, there were around 57,960 new cases[1] in 2016, and the global burden estimate will increase to more than two million new cases in 2030[2].

Most of the treatments administered to fight cancer are prepared and directed at the disease. However, the negative impacts on the patient's subjective perceptions, among them the quality of life (QoL), have increasingly been the focus of treatment. The World Health Organization (WHO) defines QoL as: "An individual's perception of his or herself, of his/her position in life within the cultural context and system of values in which he/she lives, and of his/her goals, expectations, and social standards"[3].

The main surgical and clinical approaches included in breast cancer treatment are lumpectomy and mastectomy. They may or may not be associated with axillary lymph node dissection (LA), chemotherapy (QT), radiotherapy (RT), and hormone therapy (HT)[4,5]. These approaches may cause physical and emotional consequences that worsen a patient's life, such as: wound-healing complications, alterations in sensitivity, fibroses, pain patterns, a reduction or total loss in the range of motion, a decrease in muscular strength, depression, worsening of ones' body image, damage to respiratory capacity, reduction of functional capacity, as well as lymphedema of the ipsilateral arm of the breast involved.

In addition, breast cancer treatment may generate a combined impact on the QoL and functional capacity of a patient, resulting in his or her incapacity to perform daily-life activities. Hence, physical therapy through physical rehabilitation is of utmost importance due to the support it provides for the affected limb to recover and to begin a sense of independence, which also affects QoL[6].

Therefore, through this study, we sought to evaluate the impact of physical therapy on the QoL of patients after they underwent breast cancer surgery.

METHODS

The present research is a longitudinal and prospective clinical study of convenience sampling performed from July to December of 2015. Randomly, we included patients who had undergone breast cancer surgery. They had undergone a mastectomy or quadrantectomy using an axillary approach, and received treatment at the Physical Therapy and Occupational Therapy Teaching and Care Unit (*Unidade de Ensino e Assistência em Fisioterapia e Terapia Ocupacional*—UEAFTO), which is part of the Universidade do Estado do Pará (UEPA). The Research and Ethics Committee for Human Beings from the Hospital Universitário João de Barros Barreto (CAAE: 41730415.0.0000.0017/2015) and from the UEPA (CAAE: 1.198.709-2015) approved the study. All of the participants signed a free and informed consent form.

The inclusion criteria were: patients who went to the UEAFTO, had undergone surgery less than three years prior, were older than 18, had undergone a surgery by the axillary approach, were not using antidepressants or other similar medicines, and were not receiving psychologic assistance. The following were excluded: patients with locoregional disease or a distant active disease and those that, during the evaluation, presented functional alterations. Furthermore, patients who had undergone previous physiotherapeutic treatment in order to deal with complications from breast cancer, or others that did not fit in the inclusion criteria, were excluded.

The physiotherapeutic protocol was composed of 20 sessions that were divided into two weekly sessions, with an average duration of 45 minutes per session. Patients were examined at the beginning of the treatment and after 20 sessions, based on the service assessment protocol (anamnesis and functional assessment). Then, the QV European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ C-30) and Breast Cancer Module (EORTC QLQ BR-23) questionnaires were administered[7].

The anamnesis included the patient's clinical history, such as data about the surgery, co-adjuvant treatments, and nutrition. A physical assessment was performed in which the surgical wound, the skin, the upper limb and the trunk (mass) were inspected. Each segment and possible dysfunctions were verified after surgery. The functional assessment of the scapular waist included measuring the range of motion (ROM) of both shoulders (homolateral and counter-lateral to surgery), using a goniometer in order to assess flexion, extension, abduction, adduction, and external rotation movements. The shoulder's internal rotation movements were assessed based on free active movements. We were concerned about the part of the dorsal region in which the limb positions itself: the thoracic region (without the ROM limitations), the lumbar region (mild ROM limitations) and the sacral region (severe ROM limitations). All of the movements were performed in the orthostatic position. We also performed perimetry in the upper limbs in order to verify the presence of lymphedema. The circumference was measured in six points: 14 and 7 cm above the elbow joint line; and at 7, 14 and 21 cm below the joint line, except for in the hand. The circumference was obtained when the patient sat with their shoulder flexed and their forearm extended. In addition, we also inspected and palpitated the wound-healing disorders and observed the lymphatic cords and sensorial alterations in the ipsilateral limb to surgery.

The QoL was assessed through the EORTC QLQ C-30 (appendix A) and through its specific module for breast cancer EORTC QLQ BR-23 (appendix B). Both questionnaires had already been translated and validated into Brazilian Portuguese, and their use in this study was authorized upon formal consent [7-9]. The EORTC QLQ C-30 is a questionnaire that covers specific cancer symptoms,

and includes 30 questions that are subdivided into three groups or scale domains:

- overall health condition and QoL;
- functional scales comprised of physical functioning, role function, emotional functioning, cognitive functioning, and social functioning;
- symptomatic items/scales were comprised of the following subscales: fatigue, nausea, vomiting, pain, shortness of breath, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties[10].

The EORTC QLQ BR-23 is exclusively for breast cancer and includes 23 questions that are subdivided into two scales:

- functional scale comprised of the following subscales: body image, sexual functioning, sexual pleasure and future perspectives;
- symptomatic scale with the following subscales: effects of chemotherapy, symptoms in the breast, symptoms in the arm, and concern for hair loss[10].

All of the score averages were linearly transformed into a scale from 0 to 100 points, as described in the EORTC manual. The higher the score, the better the QoL in the function scales. In the symptom scales, the higher the score, the worse the QoL. As recommended, the questionnaires were applied as interviews before and after 20 physical therapy sessions, by different researchers. The calculation followed the EORTC[7] manual.

After the first assessment had been finished, the patients were divided into three levels of attention complexity: high complexity (four patients that had a considerable shoulder ROM deficit, or a high pattern of pain and had no lymphedema), middle complexity (five patients that had lymphedema, and did or did not have pain/ ROM limitations), and low complexity (seven patients with few ROM limitations and who had mild or no pain).

The activities were done in the physical therapy outpatient clinic of UEAFTO (twice a week) and included the following: kinesiotherapy (active exercise and stretching for all the groups), with or without the support of a rod, ball or hula hoop; manual therapy (massage, pompage, passive stretching, shoulder joint mobilization, among others, for the individual group); and physiotherapeutic decongestive complex therapy (compression bandaging, active exercises, skin care, and indication of an compression elastic clamp, only for the lymphedema group). In addition, the women were given advice about home exercises, self-drainage, self-bandaging, and desensitization exercises, as well as general care regarding the superior limb ipsilateral to surgery[11].

Data were analyzed through the GraphPad Prism 6.0 software. All of the statistical tests had a significance of 5% (p<0.05). For the statistical analysis, we used Shapiro-Wilk's test to assess the distribution of data regarding QoL. The variables presented a abnormal distribution and are expressed in medians and percentiles.

We used Wilcoxon's test to make a comparison between before and after physical therapy.

RESULTS

Nineteen patients were included in the study, but only 16 were analyzed. Figure 1 presents the sample distribution. Regarding personal and clinical characteristics, our patients were 54.5 years old on average, and most were from the metropolitan region (15; 93.25%). Housewife was the most reported occupation (6/37.50%). Pre-treatment clinical staging was presented as follows:

- stage I B: two patients (12.50%);
- stage II A: six patients (37.50%);
- stage II B: four patients (25.00%);
- stage III A: four patients (25.00%).

Most of the patients had undergone a radical mastectomy (11/68.75%) by an axillary approach (11/68.75%). Patients who underwent RT only had it done in the mass. Other characteristics are found in Chart 1.

Regarding the QoL assessment scores, through the specific EORTC QLQ C-30 questionnaire, we observed, an improvement in the overall health scale domains after 20 sessions, with no statistically significant difference. Except for general function, all of the scores increased in the domain of function scales with a statistically significant difference in physical function (p<0.023), cognitive function (p<0.033), and social function (p<0.013). On the scale of the symptoms, all of the scores decreased or stayed the same, with a significant reduction in the pain (p<0.025), fatigue (p<0.001), and financial difficulty (p<0.007) subscales (Table 1).

In the specific questions regarding the EORTC QLQ BR-23 and the functional scale, we only obtained a statistically significant increase in the body image subscale (p<0.001). We did not include sexual pleasure or hair loss values, because most of the patients did not respond to either of the two scores. In the group of symptom scales, all of them decreased and had a statistically significant difference (Table 2).
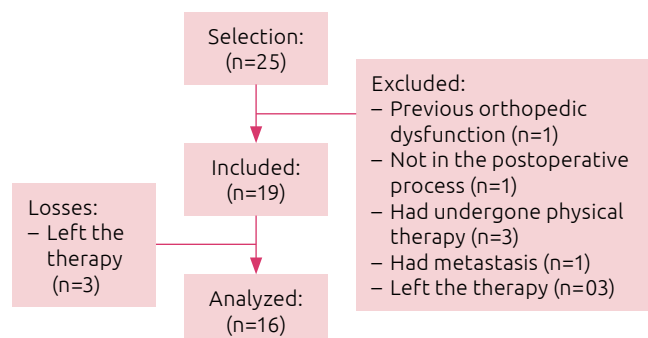
Figure 1. Flowchart of the patient selection

Chart 1. Personal and clinical-surgical characteristics.

Variable (unit)	(n=16)
Age (years)	54.5
Staging n (%)	
I B	2 (12.50)
II A	6 (37.50)
II B	4 (25.00)
III A	4 (25.00)
Origin n (%)	
Metropolitan area	15 (93.25)
Other places	1 (6.25)
Pregnancy n (%)	
Nulliparous	4 (25.00)
Pauciparous	6 (37.05)
Multiparous	6 (37.05)
Surgical procedure n (%)	
Radical mastectomy	11 (68.75)
Segmental resection	5 (31.25)
Axillary approach n (%)	
Lymph node dissection	15 (93.75)
Sentinel lymph node biopsy	1 (06.25)
Laterality n (%)	
Right breast	2 (12.50)
Left breast	14 (87.50)
Bilateral	0 (00.00)
Treatment n (%)	
Surgery+CT	6 (37.50)
Surgery+CT+RT	5 (31.25)
Surgery+CT+RT+HT	5 (31.25)
Time since surgery n (%)	
Up to 2 months	3 (18.75)
2 months to 1 year	5 (31.25)
> 1 year	8 (50.00)
Occupation n (%)	
Housewife	3 (18.75)
Maid	1 (06.25)
Farmer	1 (06.25)
Hairdresser	1 (06.25)
Fixed machinery worker	5 (31.25)
Secretary	3 (18.75)
Retired	2 (12.50)

Nulliparous: no pregnancy; pauciparous: up to two pregnancies; multiparous: more than two pregnancies; QT: chemotherapy; RT: radiotherapy; HT: hormone therapy.

DISCUSSION

A physiotherapeutic approach is currently the first choice for rehabilitation, as it is essential for the prevention and treatment of physical-functional complications[5]. This study aimed to assess the QoL of patients who had undergone breast cancer surgery, before and after their physiotherapeutic intervention. This was done through the application of two specific questionnaires (EORTC QLQ C-30 and EORTC QLQ BR-23). The results suggest that the physical therapy program improved the QoL of the patients.

The mean age of the present sample was 55 years old, which is in agreement with the estimates and findings from other studies, in which around four out of five cases occur after the age of 50[1,12].

Table 1. Comparison of the median scores of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ C-30) between the 1st and 20th physical therapy sessions (n=16).

EORTC QLQ C-30	Pre (min.-max.)	Post (min.-max.)	p-value
Overall health condition	66.67 [52.08–97.92]	79.17 [66.67–100.00]	0.246
Function scale			
Physical function	66.67 [60.00–80.00]	76.67 [61.67–93.33]	0.023*
General function	66.67 [37.70–83.33]	66.67 [50.00–95.93]	0.093
Emotional function	83.33 [39.58–91.67]	91.67 [66.67–91.67]	0.151
Cognitive function	58.34 [37.50–83.33]	83.33 [66.67–100.00]	0.033*
Social function	83.34 [66.67–100.00]	100.00 [83.33–100.00]	0.013*
Symptom scales			
Fatigue	61.12 [33.33–91.67]	16.67 [00.00–33.33]	0.001*
Pain	33.33 [16.67–50.00]	16.67 [00.00–29.17]	0.025*
Dyspnea	00.00 [00.00–33.33]	00.00 [00.00–25.00]	0.656
Insomnia	00.00 [00.00–33.33]	00.00 [00.00–33.33]	0.617
Loss of appetite	00.00 [00.00–25.00]	00.00 [00.00–33.33]	0.812
Nausea/ vomiting	00.00 [00.00–16.67]	00.00 [00.00–16.67]	0.812
Constipation	16.67 [00.00–66.67]	00.00 [00.00–58.34]	0.343
Diarrhea	00.00 [00.00–25.00]	00.00 [00.00–00.00]	0.562
Financial difficulty	33.33 [00.00–100.00]	00.00 [00.00–33.33]	0.007*

*Wilcoxon test p<0.05.

Beyond this age range, however, breast cancer cases tend to decrease, which reinforces the influence of female hormones in the disease's etiology. Most of the patients were from a metropolitan region, which makes access to health services easier. The result of a high prevalence of stay-at-home women is in agreement with studies performed by Mesquita[13] and Sousa et al.[14]. This is the case because they are probably under treatment, distant from or not able to return to their activities outside of the home.

As stated by Silva et al.[15] and Alegrance et al.[16], data from the present research shows that before beginning physical therapy, QoL was already altered. This was expected because the patient demonstrated fear of moving his/her upper limb, and pain and functional incapacity, which resulted in feelings of fragility and uselessness[17]. Problems like lymphedema, pain, paresthesia, muscle strength decrease, and ROM reduction of the involved limb are frequently observed and reported by women who have undergone breast surgery. These problems deserve attention because they interfere in the QoL of these women[4].

In a study developed by Figueiredo[18], the overall health scale improved after the physiotherapeutic intervention. However, similar to the present analysis, there was no statistically significant difference. This may be explained by the short time interval of this sample (20 sessions, around two months) and by the fact that we applied the questionnaires, and that there was a small sample. Researchers have demonstrated additional gains in up to six months of physiotherapeutic treatment. They have observed an improvement in shoulder function, in QoL and with regard to the pain of patients who had undergone LA[19].

Table 2. Comparison of median scores of the Breast Cancer Module (EORTC QLQ BR-23) questionnaire between the 1st and 20th physical therapy sessions (n=16).

EORTC QLQ BR-23	Pre (min.-max.)	Post (min.-max.)	p-value
Functional scale			
Body image	16.67 [08.33–29.17]	91.67 [61.67–100.00]	<0.001*
Sexual function	16.67 [00.00–33.33]	08.33 [00.00–33.33]	0.859
Future perspective	33.33 [08.33–66.67]	66.67 [33.33–100.00]	0.237
Symptom scales			
Systemic effects of the therapy	21.43 [5.95–37.01]	16.67 [09.52–30.95]	0.453
Arm symptoms	33.33 [22.22–80.56]	22.22 [02.77–44.00]	0.067
Breast symptoms	16.67 [10.42–31.25]	16.67 [00.00–22.92]	0.304

*Wilcoxon test p<0.05.

With regard to the function scales, all of the subscales presented an improvement, and the physical, cognitive and social functions had significant increases. Randomized and controlled studies have pointed to an improvement in ROM and functional performance of the shoulder after the completion of active exercises with free amplitude. Considering that physical function is assessed through statements like "carrying heavy shopping bags or suitcases" and "need help to eat, to dress, to wash or use the bathroom," we believe that it is related to ROM and strength improvement in addition to the fact that these women gradually return to their activities, such as getting dressed, buttoning their bras, preparing their meals, and other clothing and hygiene activities that also improve social function. Over time, women returned to their social and work activities by reinserting themselves into society[5-15].

Gradually, by returning to daily life inside the home and in the community, these patients require more physical effort to develop these basic activities. Therefore, they also require more effort to work on, not only on theses emotional and physical aspects, but also on cognitive ones, which results in the improvement of these functions and QoL[20].

With regard to the scale of symptoms, the following domains: nausea and vomit, pain, dyspnea, insomnia, weight loss, constipation and diarrhea, had low scores, indicating a good QoL. After 20 physical therapy sessions, the scores were even lower, which points to improvement in the QoL with regard to such symptoms. For these domains, the impact of physical therapy was only significant for pain.

Both pain and fatigue are the most common manifestations found in oncological patients, however these scores did not have a high incidence among the patients under treatment in our study. The results showed only a small decrease in fatigue. This may be attributed to the peculiar profile of the population being studied. Most women have a low socioeconomic level, which means they must continue with their daily activities, including work. However, in the present research, the fatigue subscale showed a statistically significant improvement in the comparison of the moments before and after the physiotherapeutic intervention. In other studies[21,22], the importance of physical therapy when following-up with women undergoing radiotherapy treatment was also demonstrated. The exercises were important for decreasing pain and fatigue, as well as avoiding the previously mentioned alterations that may compromise the performance of daily life activities and social and family contact, which may cause labor damage[23].

We also found a decrease of financial difficulty, which is in agreement with the results found in the literature[15], suggesting that this finding occurs due to the fact that patients improved their physical function and reduced symptoms and pain in their arm. Due to this improvement, usually there are fewer expenses for surgical treatment and for analgesic medicine, despite the

fact that they are patients of the Brazilian Public Health System (*Sistema Único de Saúde*—SUS), and receive pensions and benefits.

Results of the EORTC QLQ BR-23 questionnaire from the present study show that for the body image and future perspectives domains on the functionality scale, the patients improved their scores after 20 sessions. The values of the domains related to "sexual pleasure" and "hair loss concerns" were not assessed, because some patients (more than 40%) did not answer these questions. According to the recommendations in the EORTC QLQ BR-23 manual, these domains do not apply if the patient has not been sexually active or had hair fall out in the last four weeks. The lack of responses among the participants might be due to the high mean age of the sample – some patients were elderly people and therefore did not have an active sexual life. We assumed that the lack of hair loss responses was due to the small number of patients undergoing chemotherapy (which could cause this effect) during the assessment period.

The only domain that presented a statistically significant improvement was "body image". The EORTC QLQ C-30 and the EORTC QLQ BR-23 questionnaires were administered to 51 women with breast cancer in a study. They sought to observe the relation between body image, function, sexual pleasure, health, and QoL. We were able to verify that body image influences the patients' perception of their own health and the QoL[24]. In our research, we found that if QoL improves (because of physiotherapeutic post-intervention, for example), the patient's self-perception of their health progresses, and as a consequence, so does their body. Quantitative studies may not provide a full understanding of body image issues, considering that it is a subjective perception of one's own body with individual meanings for each woman, who might feel physically invaded and exteriorized because of the alterations from the therapy[14].

On the symptoms scales from the EORTC QLQ BR-23 instrument, we observed that the side effect, breast symptom and arm symptom domains had scores below 50%, which also indicate that a small level of the QoL was compromised. After the physiotherapeutic intervention, these scores were even lower, but they did not have statistically significant differences.

A restriction of the present study is the small sample size due to the limited about of time available. This also limited the number of sessions and the number of times the patients visited the outpatient clinic. We could not form a control group, because the patients who were referred to the outpatient clinic were all attended to as soon as possible. As such, it would have been unethical to prevent services from being given to a patient with symptoms and functional alterations after her breast cancer had been diagnosed, because this would harm her recovery.

CONCLUSION

According to data presented in this study, we suggest that a physiotherapeutic approach positively influences the QoL of patients after breast cancer surgery. There was a significant improvement in the EORTC QLQ C-30 questionnaire, especially with regard to the function scale, the physical function, cognitive function and social function domains, and in the pain and fatigue scale of symptoms domains. In the EORTC QLQ BR-23, we observed an improvement regarding the functional scale in the body image domain.

There is no agreement in the literature regarding the right number of sessions, but long-term follow-ups may provide additional advantages. One of the research limitations was the lack of inclusion of data concerning physical and functional assessments (perimetry, ROM) before and after treatment, which could better show the relation between an improvement in functional condition and the QoL of the patients. Studies with designs that include this data, as well as a long-term follow-up, a control group, and a larger sampling size, might offer new information for professionals involved in oncology rehabilitation services, especially for those that assist these women.

REFERENCES

1. Brasil. Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de Prevenção e Vigilância. Estimativa 2018: Incidência de Câncer no Brasil. Rio de Janeiro: INCA; 2018. 128p.

2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer [Internet]. 2010 [cited 2016 Jan 26];127:2893-917. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21351269/

3. Rett MT, Mendonça ACR, Santos RMVP, Jesus GKS, Prado VM, De Santana JM. Fisioterapia no pós-operatório de câncer de mama: um enfoque na qualidade de vida. ConScientiae Saúde. 2013;12(3):392-7. DOI:10.5585/ConsSaude.v12n3.4341

4. Lahoz MA, Nyssen SM, Correia GN, Garcia APU, Driusso P. Capacidade Funcional e Qualidade de Vida em Mulheres Pós-Mastectomizadas. Rev Bras Cancerol. 2010;56(4):423-30.

5. Silva RC. Qualidade de vida em pacientes com linfoma não Hodgkin durante a quimioterapia em regime ambulatorial: avaliação com o questionário EORTC-QLQ-C30 [dissertação]. Barretos: Fundação Pio XII – Hospital de Câncer de Barretos; 2013.

6. Leites GT, Knorst MR, Lima CHL, Zerwes FP, Frison VB. Fisioterapia em oncologia mamária: qualidade de vida e evolução clínico funcional Rev Ciênc Saúde. 2010;3(1):14-21. http://dx.doi.org/10.15448/1983-652X.2010.1.6448

7. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. On behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual. 3ª ed. Bruxelas: European Organization for Research and Treatment of Cancer; 2001.

8. Franceschini J, Jardim JR, Fernandes AL, Jamnik S, Santoro IL. Reproducibility of the Brazilian Portuguese version of the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire used in conjunction with its lung cancer-specific module. J Bras Pneumol. 2010;36(5):595-602. http://dx.doi.org/10.1590/S1806-37132010000500011

9. Michels FAS, Latorre MRDO, Maciel MS. Validity, reliability and understanding of the EORTC-C30 and EORTC-BR23, quality of life questionnaires specific for breast cancer. Rev Bras Epidemiol. 2013;16(2):52-63. http://dx.doi.org/10.1590/S1415-790X2013000200011

10. Lanza M, Bergmann A, Ferreira MGCL, Aguiar SS, Dias RA, Abrahão KS, et al. Quality of Life and Volume Reduction in women with Secondary Lymphoedema Related to Breast Cancer. Int J Breast Cancer. 2015;2015:586827. https://doi.org/10.1155/2015/586827

11. Bergmann A, Ribeiro MJB, Pedrosa E, Nogueira EA, Oliveira ACG. Fisioterapia em mastologia Oncologica: rotinas do Hospital do Câncer III/INCA. Rev Bras Cancerol. 2006;52(1):97-109.

12. Garcia SN, Jacowski M, Castro GC, Galdino C, Guimarães PRB, Kalinke LP. Os domínios afetados na qualidade de vida de mulheres com neoplasia mamária. Rev Gaúcha Enferm. 2015 Jun;36(2):89-96. http://dx.doi.org/10.1590/1983-1447.2015.02.45718

13. Mesquita FC. Perfil da mulheres encaminhadas à fisioterapia no pós-operatório de câncer de mama [dissertação]. Rio de Janeiro: Fundação Oswaldo Cruz; 2010.

14. Sousa E, Carvalho FN, Bergmann A, Fabro EAN, Dias AR, Koifman RJ. Funcionalidade de Membro Superior em Mulheres Submetidas ao Tratamento do Câncer de Mama. Rev Bras Cancerol. 2013;59(3):409-17.

15. Silva MD, Rett MT, Mendonça ACR, Silva Júnior WM, Prado VM, De Santana JM. Qualidade de Vida e Movimento do Ombro no Pós-Operatório de Câncer de Mama: um Enfoque da Fisioterapia. Rev Bras Cancerol. 2013;59(3):419-26.

16. Alegrance FC, Souza CB, Mazzei RL. Qualidade de Vida e Estratégias de enfrentamento em Mulheres com e sem Linfedema Pós-Câncer de Mama. Rev Bras Cancerol. 2010;56(3):341-51.

17. Nesvold IL, Reinertsen KV, Fossa SD, Dahl AA. The relation between arm/shoulder problems and quality of life in breast cancer survivors: a cross-sectional and longitudinal study. J Cancer Surviv. 2011;5(1):62-72. https://doi.org/10.1007/s11764-010-0156-4

18. Figueiredo SLS. Funcionalidade e Qualidade de Vida em Pacientes Submetidas à Cirurgia de Câncer de Mama [dissertação]. Belo Horizonte: Instituto de Ensino e Pesquisa Santa Casa de Belo Horizonte; 2013.

19. Beurskens CHG, van Uden CJ, Strobbe LJ, Oostendorp RA, Wobbes T. The efficacy of physiotherapy upon shoulder function following axillary dissection in breast cancer, a randomized controlled study. BMC Cancer [Internet]. 2007 [cited 2016 Jan 8];7:166-72. Available from: http://www.biomedcentral.com/1471-2407/7/166

20. Fangel LM, Panobianco MS, Kebbe LM, Almeida AM, Gozzo TO. Qualidade de vida e desempenho de atividades cotidianas após tratamento das neoplasias mamárias. Acta Paul Enferm. 2013;26(1):93-100. http://dx.doi.org/10.1590/S0103-21002013000100015

21. Seixas RJ, Kessler A, Frison VB. Atividade Física e Qualidade de Vida em Pacientes Oncológicos durante o Período de Tratamento Quimioterápico. Rev Bras Cancerol. 2010;56(3):321-30.

22. Hwang JH, Chang HJ, Shim YH, Park WH, Park W, Huh SJ, et al. Effects of supervised exercise therapy in patients receiving radiotherapy for breast cancer. Yonsei Med J. 2008;49(3):443-50. https://dx.doi.org/10.3349%2Fymj.2008.49.3.443

23. Schmidt ME, Chang-Claude J, Vrieling A, Heinz J, Flesch-Janys D, Steindorf K. Fatigue and quality of life in breast cancer survivors: temporal courses and long-term pattern. J Cancer Surviv. 2012;6(1):11-9. https://doi.org/10.1007/s11764-011-0197-3

24. Costa SR, Jimenéz F, Ribeiro JLP. Imagem corporal, sexualidade e qualidade de vida no cancro da mama. Psicol Saúde Doenças. 2012;13(2):327-39.

NIPPLE RECONSTRUCTION: DESCRIPTION AND CONTRIBUTION TO FOUR-SQUARE TECHNIQUE OR CYLINDRICAL FLAP

Reconstrução da papila mamária: descrição e contribuição à técnica do retalho *four-square* ou retalho cilíndrico

José Slaibi Filho[1,2]*, Douglas de Miranda Pires[1,3], Raffaela Levy de Andrade[3],
Carolina Nazareth Valadares[3], Carolina Lamac Figueiredo[3], Mariana dos Santos Nascimento[3]

ABSTRACT

Introduction: Techniques for breast reconstruction are becoming the new standard of care for breast cancer patients. In this context, reconstruction surgery of the nipple-areolar complex consists of an essential surgical approach to obtain a satisfactory esthetic result. Objectives: The article proposes a modification in a preexisting technique that would have less soft tissue loss and, consequently, better esthetic outcomes. Methods: Four patients underwent reconstruction of the mammary papilla with the technique proposed at Santa Casa de Ilhéus and Santa Casa de Belo Horizonte (SCBH). The technique consists of modifying the four-square flap. De-epithelialization of a lateral wing of the dermatoglossal flap is performed, which will remain in the center of the flap, providing increased central volume and increased vascularization. Results: Patients underwent nipple reconstruction with local anesthesia at least six months after breast reconstruction. They were then evaluated 30 days, 90 days and 180 days after the procedure. The volume and projection of the nipples were evaluated by photographic records. Discussion: There are numerous neo-nipple surgical descriptions, most of them presenting significant volume loss with impairment of body image. Several factors may contribute to nipple flattening after reconstruction, including the absence of natural anatomic infrastructure, inadequate vascularization of flaps, presence of centrifugal forces contrary to the reconstructed prominence, and dermal thickening of the available tissue. Conclusion: The technique detailed in the study maintains greater volume in the central part of the flap aiming to less flap volume loss and greater projection, with more satisfactory and long-lasting esthetic results. The short-term results are encouraging.

KEYWORDS: Nipples; breast neoplasms; reconstruction; mammoplasty.

RESUMO

Introdução: Técnicas de oncoplastia para reconstrução mamária têm instituído um novo padrão de cuidado no tratamento do câncer de mama. Dentro deste contexto, a cirurgia reconstrutiva da aréola e do mamilo consiste em uma abordagem cirúrgica também fundamental para obter resultado estético satisfatório. **Objetivos**: Destacar simples alteração em uma técnica já consolidada, visando menor perda tecidual e, consequentemente, melhor resultado estético. **Métodos**: quatro pacientes foram submetidas à reconstrução da papila mamária com a técnica proposta na Santa Casa de Ilhéus e Santa Casa de Belo Horizonte (SCBH). A técnica consiste na modificação do retalho four-square. É Realizada a desepitelização de uma asa lateral do retalho dermogorduroso, a qual permanecerá no centro do retalho proporcionando aumento do volume central e vascularização aumentada. **Resultados**: Pacientes foram submetidas à técnica de reconstrução do mamilo sob anestesia local pelo menos seis meses após a cirurgia mamária reconstrutiva e avaliadas após 30, 90 e 180 dias do procedimento. Foram analisados o volume e a projeção dos mamilos por meio de registros fotográficos. **Discussão**: Existem inúmeras descrições cirúrgicas de neomamilo; a maioria apresenta perda de volume significativo com prejuízo na imagem corporal. Vários fatores podem contribuir para o achatamento do mamilo após sua reconstrução, como a ausência de uma infraestrutura anatômica natural disponível, vascularização inadequada dos retalhos, presença de forças centrífugas contrárias à proeminência reconstruída e espessamento da derme disponível. **Conclusão**: A técnica pormenorizada no trabalho mantém maior volume na parte central do retalho com objetivo de haver menor perda de volume do retalho e maior projeção do neomamilo, com resultados estéticos mais satisfatórios e duradouros. Os resultados em curto prazo são animadores.

PALAVRAS-CHAVE: Mamilos; neoplasias da mama; reconstrução; mamoplastia.

INTRODUCTION

The impact of breast cancer on female scenario is not limited to its high incidence and mortality rate. The physical consequences, mainly resulting from surgical treatment, bring incalculable damages to women's self-esteem. Radical mastectomy, first described by the American surgeon William Halsted in the end of the 19th century, remained as the standard treatment for almost 100 years. Even after proposals of modified radical surgeries by Patey, Auchincloss, and Madden, only functional preservation is sought[1]. Over the last decades, breast cancer surgery approach has substantially distanced from its roots in general surgery[2]. The beginning of its new era was in the end of the 20th century, with the works of Bernard Fisher and Umberto Veronesi proposing conservative surgeries. Now, in addition to respecting oncological principles, there is also the concern with breast preservation in cases of early diagnosis. Such surgical approach, while preserving breast volume, produces deficiency in the glandular cutaneous tissue of the resected tumor area, in addition to almost always promoting deformity of the ipsilateral areola-papillary complex. The paradigms of classical oncologic surgery begin to be broken, showing more and more that female esthetics should be considered when defining the surgical scope. The preservation of women's self-esteem and the gain in quality of life starts being valued. Oncoplastic techniques for breast reconstruction became the new standard of care in breast-cancer management[3]. Werner Audretsch et al.[4] first introduced the concepts that associate both plastic and oncological surgery techniques with the aim of improving esthetic results. Despite being relatively new, this more holistic approach has increasingly gained support by the medical community dedicated to breast-cancer treatment. The reconstruction of the areola-papillary complex is a critical component of breast reconstruction process. An artistic representation of this feminine symbol of nutrition and eroticism greatly contributes to the overall impression of realism achieved after a breast reconstruction[5]. This is an integral part of breast cancer treatment after mastectomy or central quadrantectomy, helping to transform the reconstructed volume inside the breast[6]. The main objective of reconstructing the areola-papillary complex is to achieve symmetry with the contralateral side or the appearance that is closer to normal in bilateral reconstructions. The position of the new complex, new nipple projection, base, coloration and also texture are evaluated[7]. Before choosing from various techniques of mammary papilla reconstruction, one should try to deal with some problems that may arise in the handling of this surgical approach. Ideal timing of procedure should be a concern, and it may occur as the same time as breast volume reconstruction (immediate or late). Late procedure tends to be the better option, when symmetry with the contralateral breast is achieved, since the reconstructed one has its volume reduced and, consequently, its positioning alters over time.

With regard to nipple reconstruction, numerous techniques have been described in the literature in recent years. The first one, published by Berson[8], would create three triangular skin flaps that, raised and sutured, would acquire a papilla shape. The best results occur when a graft from the contralateral nipple is used, but in most cases nipples do not have right size for so. In 1984, Little created the skate flap technique, which became

widely accepted among breast surgeons. It consists of a vertical dermal-fat flap that is raised and whose lateral wings are wound around a nucleus[9]. Since Little's publication, several modifications have been proposed. Shestak and Nguyen described the double opposing flap technique, among others[10]. Other methods use local or distant-tissue grafts, alloplastic material, filling injections or combinations of these techniques[10].

Despite the wide range of techniques available in the literature, papillary projection has become relevant due to the difficulty of maintaining the results in the medium and long term. Loss of at least 50% of nipple projection after reconstructive surgeries is observed regardless of the technique used in up to two years after the procedure[6].

This work proposes a new approach to nipple reconstruction, using modifications of already established local flap techniques, in order to increase the thickness of the flap and, consequently, its vascularization. Reduction in nipple tissue loss and esthetic impairment is thus expected.

OBJECTIVE

To propose a new nipple reconstruction technique by adding a modification to the four-square flap or cylindrical flap confection. It is worth mentioning that this is a simple technique, so its accomplishment and reproducibility is very feasible.

METHOD

Patients underwent mammary papilla reconstruction with the technique proposed at Santa Casa de Ilhéus and Santa Casa de Belo Horizonte (SCBH). Three mastectomized patients and one post-centralectomy patient were evaluated. The surgeries were performed as part of the Graduate Program in Oncoplastic and Reconstructive Breast Surgery of SCBH (2015/2016). Primary breast reconstructions were performed using classic techniques such as myocutaneous TRAM flaps or skin-sparing mastectomy with prosthesis placement. (Table 1).

Nipple reconstruction was performed under sedation and local anesthesia without adrenaline, at least six months after breast reconstruction.

The new nipple was planned with the patient in orthostatic position and having the healthy breast as a guide.

Technique

After determining the nipple's center, the cylindrical or four-square flap was sketched, with dimensions having base and height variations according to the healthy breast or the patient's desire. In this way, the chosen wing was de-epithelialized, then an incision was made throughout the marked flap. The entire flap was lifted, the de-epithelialized dermal-fat wing embraced the central flap and was secured with 4.0-nylon suture. The other

dermo-epidermal wing involved the central flap and was also sutured with 4.0 nylon thread. The same thread was used to suture the central wing of the flap, while the donor area was sutured with separate stitches, stabilizing the projection acquired. It results in a nipple with good central volume and increased vascularity, which it is expected to provide minimal tissue loss in the medium and long term, with little esthetic impairment. (Figures 1 and 2).

RESULTS

This technique for the reconstruction of the areola-papillary complex was used in patients at Santa Casa de Ilhéus and Santa Casa de Belo Horizonte. Surgeries were performed between September 2015 and February 2016. Patients were evaluated 30, 90, and 180 days after the procedure. The volume and projection of the nipples were measured by photographic record.

Two cases had excellent volume and projection results after the analyzed period. In one of them, there was an approximate 20% loss of desired volume, with an acceptable esthetic result, while projection loss was superior to 50% in the other. This appears to have resulted from the patients' intrinsic comorbidities, which impaired the vascularization of the flap. Patients are currently being monitored for longer-term results.

Table 1. Selected patients (elaborated by the author).

	Age	Previous surgery
Case 1	36	TRAM
Case 2	62	Mastectomy + prosthesis
Case 3	45	Mastectomy + prosthesis
Case 4	48	Centralectomy
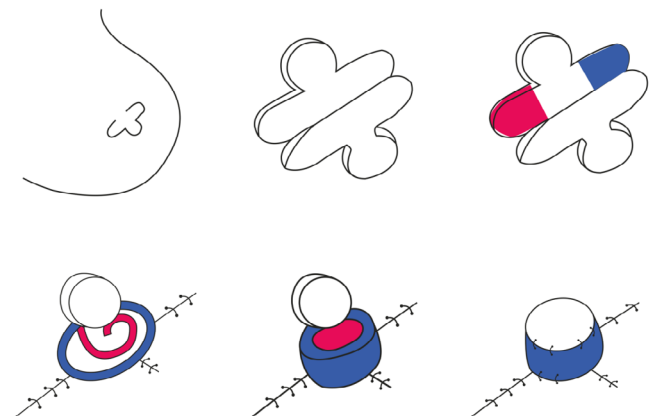
Red wing: de-epithelized area; Blue wing: epithelized area.

Figure 1. Schematic drawing for technique description (elaborated by the author).

DISCUSSION

Breast cancer surgery has changed a lot over the past few years. In view of the changes in women's social and sexual behavior along with the advances in the pharmaceutical industry, with more effective drugs and consequent increase in survival rates, these procedures require more changes. Preserving the breast, axila and their functionality is no longer enough. Women long for something beyond the biological treatment of cancer; they wish to maintain their body esthetics, femininity, and sexuality[12].

Oncoplastic and breast reconstruction surgery is a reality in several areas of Brazil. Increasingly performed by qualified breast surgeons, it greatly softens the esthetic impact of mutilation.

Several areola-papillary complex reconstruction techniques have been described, as well as the proper time to perform them. The literature shows certain consensus that the ideal time to perform this procedure should be between three and six months after breast reconstruction surgery. It is believed that this is the satisfactory time to stabilize involutive changes resulting from the surgery. Some authors have reported good results for breast volume repair using myocutaneous flaps with the technique of immediate papilla reconstruction[13,14]; others argue that immediate intervention should only be performed in bilateral cases.

The most appropriate positioning of the new papilla is another topic for discussion. Its positioning should be initially centralized within the reconstructed breast volume. Its marking should be made with the patient in supine position, mainly bilaterally, to achieve good symmetry. In unilateral cases, symmetry is more challenging and some authors recommend that the markings be performed with the patient in horizontal position; they also suggest that patients be involved in the choice of ideal spot for the papilla and encouraged to draw her own marking[6].

Another discussion point is papilla reconstruction in irradiated breasts. The undesirable effects of radiotherapy on the surgical wound have long been a cause of concern for surgeons. Vascular changes in fibroblastic activity and in growth factors, which are fundamental in the reparative process, are compromised in this situation. Some authors place previous radiotherapy as a contraindication for mammary papilla reconstruction. There are predictive factors of poor prognosis that should be evaluated in such cases to minimize undesirable outcomes: patients who had necrosis or delayed cicatrization of the mastectomy flap, fine mastectomy flaps, or history of surgical infection should not be eligible to papilla reconstruction[15]. Selection criteria should apply to patients with thicker mastectomy flaps and without clinical evidence of late radiotherapy sequelae. These guidelines, in conjunction with patient-specific assessment, should support the selection of patients with good chances of success.

The major challenge of nipple reconstruction techniques is projection maintenance.

Figure 2. Reconstruction of the areola-papillary complex using the cylindric flap in a training model (elaborated by the author).

A good esthetic result in nipple reconstruction surgery is observed using a contralateral nipple graft. However, this technique presents the low availability of adequate donor area as a limiting factor for its accomplishment[16].

Several dermal-fat flaps techniques for nipple reconstruction have been described, most of them resulting in long-term projection loss.

Several factors may contribute to nipple flattening after reconstruction, including the absence of natural anatomic infrastructure, poor vascularization of the flaps, presence of centrifugal forces contrary to the reconstructed prominence, and dermal thickening[6].

CONCLUSION

Nipple reconstruction surgery is challenging. The techniques available are varied and offer possibilities of reconstruction to women submitted to mastectomy or centralectomy.

The technique herein proposed is easy to perform and reproduce, maintaining a larger volume of tissue in the central part of the flap and, therefore, more vascularity, avoiding loss of projection. Results in the short and medium terms are encouraging.

Measurements of papillary projection should be millimetric for greater scientific validation, and further cases with longer observation periods are required so this technique is lent more credibility.

REFERENCES

1. Mora LD. História do tratamento cirúrgico do cancro da mama: empirismo e ciência. Rev Port Cir. 2013;(27):41-58.

2. Baildam AD. Oncoplastic surgery of the breast. Br J Surg. 2002;89(5):532-3.

3. Rainsbury D, Willett A. Oncoplastic breast reconstruction: guidelines for best practice [Internet]. 2012 [cited 2017 dec 5]. Avaible from: http://associationofbreastsurgery.org.uk/media/1424/oncoplastic-breast-reconstruction-guidelines-for-best-practice.pdf

4. Audretsch W, Rezai M, Kolotas C, et al. Onco-plastic surgery: target volume reduction (BCS-mastopexy), lumpectomy reconstruction (BCS-reconstruction), and flap-supported operability in breast cancer. In: Proceedings of 2nd European Congress on Senology; October 2-6, 1994; Vienna, Austria; Bologna, Italy, Moncuzzi, 1994:139-157.

5. Spear SL. Willey SC, Robb GL, Hammond DC, Nahabedian MY. Nipple-areola reconstruction. Surgery of the breast: principles and art. 2ª ed. Filadélfia: Lippincott-Raven; 2006.

6. De Lorenzi F, Lohsiriwat V. Nipple and areola complex reconstruction. In: Urban C, Rietjens M. Oncoplastic and reconstructive breast surgery. Springer, Milano; 2013.

7. Tostes RO, Silva KD, Andrade Júnior JC, Ribeiro GV, Rodrigues RB. Reconstrução do mamilo por meio da técnica do retalho c-v: contribuição à técnica. Rev Bras Cir Plást. 2005;20(1):36-9.

8. Berson MI. Construction of pseudoareola. Surgery. 1946;20(6):808.

9. Di Lamartine J, Cintra Junior R, Daher JC, Cammarota MC, Galdino J, Pedroso DB, et al. Reconstrução do complexo areolopapilar com *double opposing flap*. Rev Bras Cir Plást. 2013;28(2):233-40. DOI: 10.1590/S1983-51752013000200011

10. Sisti A, Grimaldi L, Tassinari J, Cuomo R, Fortezza L, Bocchiotti MA, et al. Nipple-areola complex reconstruction techniques: a literature review. Eur J Surg Oncol. 2016;42(4):441-65. DOI: 10.1016/j.ejso.2016.01.003

11. Ribeiro L. Reconstruções mamárias imediatas e tardias.: Cirurgia plástica da mama. 2ª ed. Rio de Janeiro: MedBook; 2012. 368 p.

12. Zucca-Matthes G. Cirurgia oncoplástica da mama. Rev Onco. 2013:36-9.

13. Williams EH, Rosenberg LZ, Kolm P, de la Torre JI, Fix RJ. Immediate nipple reconstruction on a free TRAM flap breast reconstruction. Plast Reconstr Surg. 2007;120(5):1115-24. DOI: 10.1097/01.prs.0000279142.46729.94

14. Delay E, Mojallal A, Vasseur C, Delaporte T. Immediate nipple reconstruction during immediate autologous latissimus breast reconstruction. Plast Reconstr Surg. 2006;118(6):1303-12. DOI: 10.1097/01.prs.0000244013.11974.ec

15. Draper LB, Bui DT, Chiu ES, Mehrara BJ, Pusic AL, Cordeiro PG, et al. Nipple-areola reconstruction following chest-wall irradiation for breast cancer: is it safe? Annals Plastic Surgery. 2005;55(1):12-5. DOI: 10.1097/01.sap.0000168037.87942.b5

16. Biazuz JV, Zucatto AE. Cirurgia da mama. Porto Alegre: Artmed; 2005.

17. Zucca-Matthes G. Cirurgia oncoplástica da mama. Rev Onco. 2013:36-9.

18. Williams EH, Rosenberg LZ, Kolm P, de la Torre JI, Fix RJ. Immediate nipple reconstruction on a free TRAM flap breast reconstruction. Plast Reconstr Surg. 2007;120(5):1115-24. DOI: 10.1097/01.prs.0000279142.46729.94

19. Delay E, Mojallal A, Vasseur C, Delaporte T. Immediate nipple reconstruction during immediate autologous latissimus breast reconstruction. Plast Reconstr Surg. 2006;118(6):1303-12. DOI: 10.1097/01.prs.0000244013.11974.ec

20. Draper LB, Bui DT, Chiu ES, Mehrara BJ, Pusic AL, Cordeiro PG, et al. Nipple-areola reconstruction following chest-wall irradiation for breast cancer: is it safe? Annals Plastic Surgery. 2005;55(1):12-5. DOI: 10.1097/01.sap.0000168037.87942.b5

21. Biazuz JV, Zucatto AE. Cirurgia da mama. Porto Alegre: Artmed; 2005.

PATIENT SELECTION AND TRANSVERSE RECTUS ABDOMINIS MYOCUTANEOUS FLAP COMPLICATIONS: A LITERATURE REVIEW

Seleção de pacientes e complicações do retalho miocutâneo
do músculo reto abdominal: revisão de literatura

Raissa Cruz Oliveira[1]*, Douglas de Miranda Pires[2], Carolina Nazareth Valadares[3],
Guilherme Junqueira Souza[3], Mariana dos Santos Nascimento[3], Ana Carolina Guglielmelli Mendonça[3]

ABSTRACT

Introduction: Breast cancer is the most prevalent malignant neoplasm in women. Due to delayed diagnosis, a modified radical mastectomy is the surgical treatment of choice for a large proportion of patients with the disease. Breast reconstruction with myocutaneous flaps is the technique that offers the best long-term results. The TRAM (transverse rectus abdominis myocutaneous) technique has been improved in the last 30 years, and its main advantage is its use of large volumes, which gives the new breast contour and a more natural consistency. Objective: Review the literature on the reconstruction technique with the TRAM flap, focusing on technique, patient selection and the main complications. Results: The main indications regarding reconstruction with TRAM refer to cases with extensive defects after immediate or delayed mastectomy, or when there are major consequences from radiotherapy or failure in other reconstructions. Strict criteria must be adopted in the selection of these patients, especially with regard to their comorbidities. The proper selection of patients can reduce a series of complications arising from the method. Conclusion: TRAM is an excellent option for immediate or delayed breast reconstruction as long as the patients are well selected. It eliminates (or at least reduces) the need for implants and their possible implications and additionally gives a more natural format to the reconstructed breast by accompanying the patient's weight fluctuations. However, this technique is not free of complications, especially with regard to donor areas and the patient's need for longer surgical and recovery time.

KEYWORDS: Myocutaneous flap; breast.

RESUMO

Introdução: O câncer de mama é a neoplasia maligna mais prevalente em mulheres. Em decorrência do diagnóstico tardio, a mastectomia radical modificada permanece como o tratamento cirúrgico de escolha para grande parte das pacientes portadoras da doença. A reconstrução mamária com retalhos miocutâneos apresenta os melhores resultados em longo prazo. A técnica do TRAM foi aperfeiçoada nos últimos 30 anos e tem como principal vantagem a utilização de grandes volumes, dando à nova mama contorno e consistência mais naturais. Objetivo: Revisar a literatura a respeito da técnica de reconstrução com o TRAM, enfocando as indicações da técnica, a seleção de pacientes e suas principais complicações. Resultados: As principais indicações da reconstrução com TRAM referem-se a casos de defeitos extensos após mastectomia imediata ou tardiamente, ou quando existem sequelas importantes de radioterapia ou falha em outras reconstruções, devendo-se ter critérios rigorosos na seleção dessas pacientes, principalmente no que diz respeito às suas comorbidades. A adequada seleção de pacientes pode reduzir uma série de complicações advindas do método. Conclusão: O TRAM é uma excelente opção para a reconstrução mamária imediata ou tardia, desde que as pacientes sejam bem selecionadas; elimina (ou, pelo menos, reduz) a necessidade de implantes e suas possíveis implicações, além de dar formato mais natural à mama reconstruída, acompanhando as flutuações de peso da paciente. Entretanto, essa técnica não está isenta de complicações, principalmente na área doadora, além de demandar tempo cirúrgico e de recuperação maiores.

PALAVRAS-CHAVE: Retalho miocutâneo; mama.

INTRODUCTION

Breast cancer is the type of cancer that most affects women in Brazil and around the world. Because of its high incidence, this neoplasm is a major public health concern, especially because of the psychological and social impacts it has on women. Living with a stigma-related illness, suffering prejudice, and constantly living with uncertainties and the likelihood of recurrence are extremely distressing situations.

The surgical treatment of breast cancer has changed a lot in recent decades. Nevertheless, due to delayed diagnosis, a modified radical mastectomy continues to be the most performed intervention. The removal of this organ, in conjunction with adjuvant therapies, contributes to the development of physical complications and psychological disorders that negatively influence the patient's quality of life[1,2].

Missing a breast alters a woman's body image and produces a feeling of mutilation, and loss of femininity and sensuality. In an attempt to reduce the negative feelings triggered by the disease and its treatment, to improve self-esteem, to supplement the lack of breast and to facilitate getting dressed, breast reconstruction has gained more and more momentum, taking on an important role. It is a safe procedure that does not increase the risk of recurrence of the disease, does not interfere with its detection, and does not delay adjuvant therapies[1,2].

Although 35-40% of women diagnosed annually with breast cancer undergo a complete mastectomy, historically less than 25% of them undergo immediate reconstruction[3-5].

There are several breast reconstruction techniques, including procedures with local flaps and mammoplasty, the use of alloplastic materials (tissue expanders and prostheses), autologous flaps, in addition to combined techniques. No procedure is superior to the others in all matters, however, the patient benefits when there is a meticulous choice made based on the surgeon's experience, the patient's desires and, mainly, the indications and contraindications of each technique.

Breast reconstruction has made great progress in the last few decades due to the improvement and the development of new techniques. A better understanding of the anatomy of cutaneous vascularization, associated with the transfer of vascularized tissues at a distance, gave surgeons new options for the treatment of patients with breast cancer[6]. In this context, the use of myocutaneous flaps - in particular the rectus abdominis muscle flap (TRAM) - is prominent among modern reconstructive surgery and has become the most commonly used autogenous tissue donor area for breast reconstruction[7-11].

In 1977, Drever published the first version of the vertical rectus abdominis report[12]. In 1979, Holmström[13] first used TRAM for breast reconstruction. In the same year, Robbins[14] described this flap as a pedicle. However, the method was only popularized in 1982 by Hartrampf et al.[15], who first described the TRAM pedicle flap for breast reconstruction.

The TRAM flap offers numerous benefits over conventional techniques. It allows for the use of large volumes and greater flexibility in the assembly of the flap. It gives the new breast more natural contours and consistency. It produces better long-term results and eliminates (or at least reduces) the necessity of using implants[7,16,17]. More than 90% of women demonstrate satisfaction with the aesthetic result provided by the TRAM technique[18].

TRAM is considered the technique of choice for breast reconstruction with autologous tissue, and does not seem to reduce the effectiveness of oncologic treatment[8,19].

Although it is a very accepted procedure, there still exist complications, which continue to be a problem in breast reconstruction.

The complications associated with breast reconstruction using TRAM can be grouped into two categories: relating to the flap and relating to the donor area. Systemic complications, such as deep venous thrombosis, pulmonary embolism, infection or loss of fluids will not be described in this study.

The objective of this study was to review the literature on the TRAM flap technique, emphasizing the main indications with regard to the method, the selection of patients and the main complications.

MATERIALS AND METHODS

A bibliographical survey was performed in books and electronic databases, including SCIELO, LILACS and PUBMED, with the descriptors: TRAM Flap, Breast Reconstruction, Oncoplastic Breast Surgery, Indications, and Complications. We found a total of 62 articles. Those included in the review were published after the year 2000 and were clearly associated with the proposed subject matter. They were selected by reading the title and the abstract. Articles that did not meet the above inclusion criteria were excluded.

RESULTS AND DISCUSSION

A description of the technique

The TRAM flap consists of the use of excess skin and tissue from the infraumbilical region on the rectus abdominis muscle in conjunction with the muscle. As such, it allows for the re-sectioning of large volumes. To have a flap, it is necessary to have a receiving area - which is the site of a previous mastectomy - and a donor area with good vascularization. When preparing the recipient area, the preservation of the inframammary fold is essential to make a shape that is symmetrical to the contralateral breast, in addition to a mammary storage place to receive the flap adequately and sufficiently. The anatomical concept of TRAM is based on the superior epigastric arteries, which allow for flap irrigation.

The donor region is defined by the cutaneous fold formed, which starts from the suprapubic region and goes up until both

the anterior-posterior iliac crests. The ends of these lines attach to another line, passing through the upper border of the umbilical scar. Thus, the donor area appears to be an ellipse of dermal fat tissue in the infraumbilical region. Defining the donor area depends basically on its irrigation. Initially, Hartrampf et al.[15] divided the lower abdomen into four zones: the first, referring to the rectus abdominis muscle; the second, referring to the region on the contralateral rectus abdominis muscle; the third, the lateral portion of the flap ipsilateral to the chosen muscle; and the fourth, the portion of the most distant flap in the contralateral region.

Contemporary studies have shown the best perfusion in the zone ipsilateral to the rectus abdominis muscle of interest in relation to the contralateral region of the flap. As such, the interval between zones II and IV[20] is suggested. Therefore, it is believed that the best irrigation of the lower abdominal flap is first performed by the perforating vessels coming out directly from the abdominal muscle (zone I), followed by the adjacent ipsilateral lateral region (zone II), the adjacent contralateral region (zone III) and finally by the contralateral lateral portion of the flap (zone IV). This area (zone IV) should be neglected in most single-pedicle reconstructions because of their low perfusion.

The rectus abdominis muscle can be chosen on either side or even used bilaterally as needed. The ipsilateral vascularization in single-pedicle flaps is better than in contralateral ones and, in addition, there is an improvement in the aesthetic result of the abdominals, because it avoids epigastric bulging of the rotating muscle. Either way, each case requires that the surgeon perform a thorough study to define the best options and the best plan for the patient. It is noteworthy that the dermal tunnel upon being prepared - and where the pedicled flap will be displaced - should be located in the medial portion of the inframammary sulcus. It will communicate the recipient storage with the upper abdomen.

The venous drainage is made by the superior and inferior epigastric veins, which anastomose by inosculation inside the muscle. The presence of valves in the deep venous system is described. They are faced upwards in the superior veins and face downward in the inferior veins. This fact could cause drainage damage of the flap when raised with a superior pedicle. Denervation of the rectus abdominis is inevitable and causes muscle atrophy. It happens from the last intercostal branches and by the ileo-hypogastric nerve. The flap is de-epithelialized and excess tissue is discarded. The abdominal wall is reconstructed with a Márlex® screen, and suction drains are placed in the breast and abdomen.

Indications and the selection of patients

Reconstruction with TRAM is indicated in cases of extensive defects after a mastectomy - in immediate reconstructions, when there is a need for a large replacement of skin after a mastectomy, and in the delayed ones, when there is need for skin or when there are severe consequences of radiotherapy in the thoracic wall. Furthermore, the procedure is indicated in cases with a failure in reconstruction with prostheses - as in cases of severe capsular contracture or implant loss. Finally, it is indicated in cases with a failure in reconstruction with a large dorsal flap and in patients with a protruding abdomen and who have a preference for the technique.

Patients with prior surgery in the upper abdomen and who have lesions of the superior deep epigastric vessels - such as open cholecystectomy - or surgeries that injure the subcutaneous perforation of the flap - such as abdominoplasty and very extensive liposuction, are not recommend to have the procedure. Additionally, those that do not have a sufficient donor area, wish to become pregnant, have decompensated diabetes or are morbidly obese, are not indicated for the procedure.

Patients that smoke are at an increased risk of superficial necrosis of the flap, abdominal necrosis and hernias, when compared to nonsmokers[21,22]. Eberlein et al. described 7% of partial losses in 101 patients submitted to TRAM reconstruction. All losses correlated with heavy smoking[23]. When patients stop smoking at least three weeks before surgery, the incidence of complications decreases significantly[22].

Relative contraindications may be related to the patient's activities. For example, sports and work activities that require the use of physical strength should be evaluated with caution. Comorbidities such as vasculopathies, diabetes, collagenases, obesity, chronic debilitating diseases, and inability to withdraw from usual activities for a long period of time are also considered to be contraindications.

Complications

One of the major advantages of using the TRAM flap is that it does not require the use of a prosthesis, thus avoiding many of the complications associated with the procedure, such as infection, capsular contracture, exteriorization and possible need for a posterior replacement[24,25].

As a reconstruction technique that exclusively uses autologous tissue, the TRAM flap allows for a more natural breast with regard to touch and appearance[8,24-27]. Moreover, it alters its size with variations in weight[10,24], just as it would with the normal breast[24] in the course of the aging process[9].

Furthermore, it requires a smaller number of procedures to revise and restore symmetry of the breasts when compared to prosthetic reconstruction techniques[11]. In this surgical technique, the patient is submitted to an abdominoplasty with transposition of the navel (determined by the way the tissue is removed for reconstruction), which may be pleasing to many because it improves the contour of the abdominal region[24,28]. This procedure usually results in a scar that is scarcely visible and can be kept in a very low position, near the pubic symphysis[8].

With regard to the complications resulting from the technique, they may affect the donor area or the flap used in the

reconstruction. As for donor area morbidity, complications such as abdominal hernias, bulging, abdominal wall rejection or infection, dehiscence, weakness of the abdominal wall and its interference with daily activities have been debated since the introduction of TRAM[19,29-31].

According to Ascherman et al., the rates of abdominal complications resulting from the use of TRAM are low, and as such, the procedure continues to be a good option for women seeking breast reconstruction[25]. The bipedicule flap is safer in relation to its vascularization, but it results in higher rates of donor area complications.

With regard to the morbidity of the flap, compromising its vascularization is perhaps the greatest fear, since it involves the rotation of a pedicled flap, which can occur both through irrigation deficiency and through venous stasis. This impairment may occur to varying degrees, from a small portion of dehiscence of the surgical borders to partial or complete necrosis of the flap. In addition, hematoma formation and infection may occur.

Patients with a history of smoking, in addition to patients that are diabetic, obese or overweight are at an increased risk of complications of the flap[9,32]. This technique can only be used when there is enough abdominal fat to rebuild the breast.

In very thin patients, the use of flaps from the abdomen is not a good choice[24].

The use of a TRAM flap involves a more complicated surgery. It is more time consuming and results in greater blood losses. Thus, hospitalization and the postoperative recovery period are generally longer than in other reconstruction techniques[19,28-31]. Patients are hospitalized for five to seven days. Returning to usual activities may take two to four months[9].

CONCLUSION

Although autologous breast reconstruction using TRAM has longer surgical and recovery time, the technique usually requires fewer revisions and procedures to make the breasts symmetrical. Additionally, it is considered to be oncologically safe and have few serious complications.

TRAM is an excellent method for breast reconstruction in previously selected patients, since, at first, it does not require the use of implants and gives the reconstructed breast a very similar appearance to that of a natural breast.

Appropriate selection is the main key to the success of the surgery, for it is important to consider the patient's desire and lifestyle, as well as the presence of associated pathologies.

REFERENCES

1. Oliveira RR, Morais SS, Sarian LO. Efeitos da reconstrução mamária imediata sobre a qualidade de vida de mulheres mastectomizadas. Rev Bras Ginecol Obstet. 2010;32(12):602-8.

2. Oliveira Junior FC, Mélega JM, Pinheiro AS, Pereira RF. Reconstrução mamária total: técnicas e complicações. Rev Bras Cir Plást. 2010;25(suppl.1):62.

3. Albornoz CR, Bach PB, Mehrara BJ, Disa JJ, Pusic AL, McCarthy CM, et al. A paradigm shift in U.S. Breast reconstruction: increasing implant rates. Plast Reconstr Surg. 2013;131(1):15-23.

4. Nano MT, Gill PG, Kollias J, Bochner MA, Malycha P, Winefield HR. Psychological impact and cosmetic outcome of surgical breast cancer strategies. ANZ J Surg. 2005;75(11):940-7.

5. Atisha D, Alderman AK, Lowery JC, Kuhn LE, Davis J, Wilkins EG. Prospective analysis of long-term psychosocial outcomes in breast reconstruction: two-year postoperative results from the Michigan Breast Reconstruction Outcomes Study. Ann Surg. 2008;247(6):1019-28.

6. Munhoz AM, Duarte G, Ishida L, Cunha M, Ferreira MC. Reconstrução mamária pós-mastectomia com tecido autógeno – Avaliação comparativa de resultados e complicações. Rev Ginecol Obstet. 2002;13:60-6.

7. De Lorenzi F, Brenelli F, Thomazini MV. Reconstrução mamária com retalhos miocutâneos. In: Boff RA, Carli AC, Brenelli H, Brenelli FP, Carli LS, Sauer FZ, et al. Compêndio de Mastologia: Abordagem multidisciplinar. Caxias do Sul: Lorigraf; 2015. p.567-80.

8. Petit J, Rietjens M, Garusi C. Breast reconstructive techniques in cancer patients: which ones, when to apply, which immediate and long term risks? Crit Rev Oncol Hematol. 2001;38:231-9.

9. Hu E, Alderman AK. Breast reconstruction. Surg Clin North Am. 2007;87:453-67.

10. Mandrekas AD, Zambacos GJ, Zervoudis S. Tram flap breast reconstruction and weight fluctuations: it is alive! Plast Reconstr Surg. 2003;112:696-7.

11. Kroll SS, Baldwin B. A comparison of outcomes using three different methods of breast reconstruction. Plast Reconstr Surg. 1992;90:455-62.

12. Drever JM. The epigastric island flap. Plast Reconstr Surg. 1977;59(3):343-6.

13. Holmström H. The free abdominoplasty flap and its use in breast reconstruction. An experimental study and clinical case report. Scand J Plast Reconstr Surg. 1979;13(3):423-7 .

14. Robbins TH. Rectus abdominis myocutaneous flap for breast reconstruction. Aust N Z J Surg. 1979;49(5):527-30.

15. Hartrampf CR, Scheflan M, Black PW. Breast Reconstruction with a Transverse Abdominal Island Flap. Plast Reconstr Surg. 1982;69:216-25.

16. Munhoz AM, Ferreira MC. Reconstrução Mamária com Microcirurgia. In: Pinotti JA, ed. Tratado de Ginecologia. São Paulo: Revinter; 2004.

17. Brenelli F, Urban C, Frasson R, Frasson A. Reconstrução mamária com retalhos miocutâneos. In: Frasson A, Novita G, Millen E, Zerwes F, Brenelli F, Urban C, et al. Doenças da Mama: guia de bolso baseado em evidências. São Paulo: Atheneu; 2013. p.277-83.

18. Parker PA, Youssef A, Walker S, Basen-Engquist K, Cohen L, Gritz ER, et al. Short-term and long-term psychosocial adjustment and quality of life in women undergoing different surgical procedures for breast cancer. Ann Surg Oncol. 2007;14:3078-89.

19. Nahabedian MY, Momen B. Lower abdominal bulge after deep inferior epigastric perforator flap (DIEP) breast reconstruction. Ann Plast Surg. 2005;54:124-9.

20. Holm C, Mayr M, Höfter E, Ninkovic M. Perfusion zones of the DIEP flap revisited: a clinical study. Plast Reconstr Surg. 2006;117(1):37-43.

21. Fernandéz-Frias AM, Aguilar J, Sánchez JA, Merck B, Piñero A, Calpena R. Immediate reconstruction after mastectomy for breast cancer: which factors affects its course and final outcome? J Am College Surg. 2009;208(1):126-33.

22. Chang DW, Reece GP, Wang B, Robb GL, Miller MJ, Evans GR, et al. Effect of smoking on complications in patients undergoing free TRAM flap breast reconstruction. Plastic Reconstructive Surg. 2000;105:2374-80.

23. Eberlein TJ, Crespo LD, Smith TL, Hergrueter CA, Douville L, Eriksson E. Prospective evaluation of immediate reconstruction after mastectomy. Ann Surg. 1993;218:29-36.

24. Djohan R, Gage E, Bernard S. Breast reconstruction options following mastectomy. Cleve Clin J Med. 2008;75(Suppl 1):S17-23.

25. Ascherman JA, Seruya M, Bartsich SA. Abdominal wall morbidity following unilateral and bilateral breast reconstruction with pedicled TRAM flaps: an outcomes analysis of 117 consecutive patients. Plast Reconstr Surg. 2008;121:1-8.

26. Saulis AS, Mustoe TA, Fine NA. A retrospective analysis of patient satisfaction with immediate postmastectomy breast reconstruction: comparison of three common procedures. Plast Reconstr Surg. 2007;119:1669-76; discussion 1677-8.

27. Alderman AK, Kuhn LE, Lowery JC, Wilkins EG. Does patient satisfaction with breast reconstruction change over time? Two-year results of the Michigan Breast Reconstruction Outcomes Study. J Am Coll Surg. 2007;204:7-12.

28. Kronowitz SJ, Kuerer HM. Advances and surgical decision-making for breast reconstruction. Cancer. 2006;107:893-907.

29. Spear SL, Mardini S, Ganz JC. Resource cost comparison of implant-based breast reconstruction versus TRAM flap breast reconstruction. Plast Reconstr Surg. 2003;112:101-5.

30. Blondeel N, Vanderstraeten GG, Monstrey SJ, Van Landuyt K, Tonnard P, Lysens R, et al. The donor site morbidity of free DIEP flaps and free TRAM flaps for breast reconstruction. Br J Plast Surg. 1997;50:322-30.

31. Blondeel N, Boeckx WD, Vanderstraeten GG, Lysens R, Van Landuyt K, Tonnard P, et al. The fate of the oblique abdominal muscles after free TRAM flap surgery. Br J Plast Surg. 1997;50:315-21.

32. Thorne CH, Beasley RW, Aston SJ, Bartlett SP, Gurtner GC, Spear SL. Breast Reconstruction: TRAM Flap techniques. In: Thorne CH, editor. Grabb and Smith's Plastic Surgery. 6ª ed. Philadephia: Lippincott Williams & Wilkins; 2007. p.641-7.

REDUCTION MASTOPLASTY AND ITS HISTOPATHOLOGICAL FINDINGS AT SANTA CASA DE BELO HORIZONTE

Mastoplastia redutora e seus achados histopatológicos na Santa Casa de Belo Horizonte

Douglas de Miranda Pires[1], Alessandro Cesário da Silveira[2]*,
Guilherme Junqueira Souza[3], Carolina Nazareth Valadares[3], Izabel Aparecida Cunha Andrade[3]

ABSTRACT

Introduction: Reduction mammoplasty surgery aims to obtain an aesthetic and postural balance in patients, and is among the most performed aesthetic surgeries in Brazil. Objective: This study analyzed 181 pathological results of patients aged between 17 and 57 years old, who underwent breast reduction at Santa Casa de Misericórdia de Belo Horizonte. Methodology: A retrospective study of anatomopathological exams of surgical specimens was carried out, and the acquired data were compared to data available in the literature. Results: The analysis showed that most patients from the study had benign pathological findings. Most of them had increased fibroadipose stroma (81.21%), while 9.9% had adenosis, 7.7% had fibrocystic changes,3.3% had columnar cell changes, and 7.18% had breast metaplasia. Conclusion: There is a high prevalence of conditions that require breast reduction and, because of that, it was concluded that benign breast diseases are the main cause of visits to the breast specialist's office. Thus, it is important for breast surgeons to be familiar with them and be aware of differential diagnosis, rather than malignancy. The majority of benign diseases can be monitored clinically and with imaging exams. Pathological diagnosis is necessary when there is suspicion of malignancy in imaging methods and clinical examination.

KEYWORDS: Mammoplasty; pathology; hypertrophy; breast.

RESUMO

Introdução: A mamoplastia redutora visa a obter o equilíbrio estético e postural nas pacientes e está entre as cirurgias estéticas mais realizadas no Brasil. Objetivo: Este trabalho analisou resultados de 181 exames histopatológicos de pacientes na faixa etária entre 17 e 57 anos submetidas à mamoplastia redutora na Santa Casa de Misericórdia de Belo Horizonte, pela equipe de mastologia. Metodologia: Foi realizado um estudo retrospectivo de exames anatomopatológicos de peças cirúrgicas e os dados adquiridos foram comparados aos dados disponíveis na literatura. Resultados: Praticamente todas as pacientes submetidas à mamoplastia redutora apresentaram achados considerados benignos. A maioria das pacientes apresentou estroma fibroadiposo aumentado (81,21%), enquanto 9,9% apresentaram adenose; 7,7% alterações fibrocísticas; 3,3% alterações de células colunares e 7,18% metaplasia mamária. Conclusão: Devido à grande prevalência das afecções que necessitam de mastoplastia redutora, concluiu-se que as doenças mamárias benignas correspondem à maior parte das queixas mamárias do dia a dia do mastologista. Dessa forma, é importante saber defini-las com precisão, ter conhecimento dos diagnósticos diferenciais e excluir a malignidade. A grande maioria dessas afecções pode ser acompanhada clínica e/ou imaginologicamente. O diagnóstico histopatológico é necessário quando a lesão for suspeita aos métodos de imagem ou ao exame clínico.

PALAVRAS-CHAVE: Mamoplastia; patologia; hipertrofia; mama.

INTRODUCTION

Mammary hypertrophy is a body contour deformity characterized by the presence of bulky breasts that are disproportionate to the patient's biotype, and which may or may not be ptosed. This dysmorphia can cause mastalgia, back pain, postural defects, respiratory distress and the limitation of physical activities, which is a frequent complaint in breast specialists' or plastic surgeon's offices. The treatment for this disease is surgical. According to the weight of the breast tissue being removed through surgery, it can be classified as mild (up to 500 g), moderate (501 to 800 g), severe (801 to 1,000 g) and gigantomastia (greater than 1,000 g). In most cases, it can be observed that the greater the degree of breast hypertrophy, the greater the discomfort for the patient, and the greater the difficulty of self-examination for the detection of illnesses[1].

Reduction mammoplasty, a surgery whose goal is to obtain aesthetic and postural balance for patients with macromastia, congenital mammary asymmetry or symmetrization after contralateral mastectomies, is among the most performed aesthetic surgeries in Brazil[2-5].

The increase in the incidence of breast cancer has been accompanied by an increase in mortality, which can be attributed mainly to a delay in diagnosis and lack of appropriate treatment. In Brazil, 70% of the diagnosed cases are in more advanced stages (III and IV), when the patients' survival and cure rates are substantially lower. In this context, the preoperative evaluation of patients who are candidates for corrective mastoplasty may be an important opportunity to identify clinical/imaging findings that may guide an investigation of neoplastic problems. This includes the possibility of having previously planned oncological treatment and not necessarily having to give up the corrective purpose of breast hypertrophy. The concept of oncoplastic surgeries encompasses this option responsibly. In addition, candidates for this procedure should also be submitted to a histopathological evaluation of the tissue specimens in the postoperative period in order to identify possible changes, be they benign or malignant, since 60% of patients without changes in the preoperative period presented benign changes in surgical pieces of mammoplasties[4]. The finding of incidental mammary carcinoma corresponds to only 0.05 to 1.66% of the patients submitted to reductive mammoplasty[6].

Several studies have observed a higher incidence of histological alterations in surgical specimens from this type of intervention and discuss the real importance of these exams[4,5,7,8].

Among these alterations, malignant pathologies can also be diagnosed[3], justifying a detailed approach in the pre-operative clinical and radiological evaluation.

This study aimed to analyze the results of histopathological examinations of patients submitted to reduction mammoplasty at Santa Casa de Misericórdia de Belo Horizonte, comparing them to those available in the literature.

METHODOLOGY

A retrospective study of anatomopathological examinations of surgical pieces from reduction mammoplasty performed at the above hospital was carried out in the period from June 2012 to February 2016. The sample consisted of 181 patients, aged between 17 and 57 years old. All of them underwent the clinical investigation process as directed by the Brazilian Mastology Society with physical and imaging examination according to their age group to detect breast cancer and suspected lesions.

The patient's age, the weight of the resection area of the two breasts together, and the histopathological results of each patient were considered.

Statistical analysis was performed with software SPS S for Windows ver. 16.0 (PASW SPSS Software ver. 18) (SPSS, Inc., Chicago, IL).

RESULTS

The data were obtained by means of 181 reports of anatomopathological exams, filed in the mentioned institution, and distributed as follows:

- 30 for the year 2012;
- 52 for the year 2013;
- 55 for the year 2014;
- 43 for the year 2015; and
- 1 for the year 2016.

The study population consisted of 181 women aged between 17 and 57 years old (mean: 33.14 years old).

The weight of the pieces ranged from 18 to 2,620 g (mean: 808.22 g).

In the present study, the majority of patients submitted to reduction mammoplasty had increased fibrous stroma (81.21%), while 9.9% had adenosis, 7.7% had fibrocystic alterations, 3.3% had alterations of columnar cells, and 7.18% had mammary metaplasia.

DISCUSSION

The evaluation of proliferative lesions in the pieces studied can individualize patients and define strategies for follow-up or preventive measures, such as the use of antiestrogens and risk-reducing mastectomy, or a more careful clinical follow-up[4]. Some patients may present important microscopic lesions, even if radiological examinations show no alterations[9], thus showing the importance of sending all the surgical pieces for histopathological study.

In the study by Barros[5], the majority of patients submitted to reductive mammoplasty had no alterations upon the anatomopathological study, and the fibrocystic alterations were the only statistically significant finding among the groups, with 76.2% of the cases. Women over 35 years of age had greater alterations than those that were younger. In the present study, the

fibrocystic alterations comprised only 7.7% of the cases, and the majority showed increased fibrotrophic stroma (81.21%). In the study by Bittencourt et al.[3], 26 patients had fibrocystic alterations, 11 patients had stromal fibrosis, 21 patients had lipomastia and stromal fibrosis, and the other patients had similar alterations. The study by Tafuri and Gobbi[2] also detected a greater number of fibrocystic alterations. Cysts and ductal ectasia were present in 50.9% of bilateral aesthetic reduction mammoplasties and in 59.7% of contralateral mammoplasties.

Other works have indicated the insignificant presence of ductal carcinoma *in situ*[3,5,7] and lobular carcinoma *in situ*[4]. In 1998, Jansen et al. published a survey on hidden breast cancer in 0.16% of 2,576 mammoplasties[10]. Desouki et al., in 2013, reported two (0.08%) cases of invasive carcinomas in surgical pieces of 2,498 breast reductions[11]. In 2012, Hassan et al. reported nine cases (0.65 %) of carcinoma out of a series of 1,388 mammoplasties.[12]

All of these malignant findings were incidental in patients with imaging tests that presented no suspected abnormalities. These studies reflect a low rate of detection of occult cancer in reduction mammoplasty specimens in years, which is explained by the progress in population education, the younger group of patients performing breast surgery and more complete preoperative screening.[6]

There were no references in the literature that related the degree of breast hypertrophy to the sensitivity and specificity tests of the imaging exams.

It was stated that in patients older than 40 years old or submitted to mammary reduction for symmetrization after mastectomy, the histological examination of the surgical specimens is scientifically reinforced[4]. For Souza et al.[8]; Barros[5] and

Sugita[7], the group aged above 35 years old seems to benefit from this practice due to the care instituted in the monitoring and/or treatment of patients, as a result of the diagnoses performed with such a routine.

In the present study, the most common finding was increased fibroadipose stroma. Despite the peculiarities in the description of the reports of alterations in the studied specimens, we observed a coincidence with the literature on the histopathological diagnoses, especially when it comes to benign findings. In this study, there were no cases of malignancy, atypia, or precursor lesions for comparison.

One of the limitations of this study is that there was no standardization of histopathological reports, which may have led to differences in the proportions of the diagnoses. However, there was no doubt as to the differentiation between benignity and malignancy.

CONCLUSION

All the patients in our study presented alterations in the anatomopathological examination, the benign non-proliferative changes of the breast were the main findings. The occurrence of occasional carcinoma in reduction mammoplasty, despite the low incidence, can occur, even when preoperative examination results are considered normal.

In this study, the majority of patients presented increased fibrotrophic stroma and there was no case of malignancy, different from the reviewed literature. However, due to the high prevalence and increasing incidence of breast cancer, a complete evaluation of women candidates for the reduction mammoplasty procedure is mandatory.

REFERENCES

1. Moceline PR, Martins OJ, Brito LM. Souza RD, Pinheiro GL, Duarte TB, et al. Hipertrofia de mama: estudo comparativo dos achados histopatológicos e de imagem. Rev Bras Mastologia. 2011;21(4):148-52.

2. Tafuri LS, Gobbi H. Hiperplasias epiteliais em espécimes de mamoplastia redutora estética bilateral e mamoplastia redutora contralateral a câncer de mama. J Bras Patol Med Lab. 2005;41(2):133-38. DOI: 10.1590/S1676-24442005000200012

3. Bittencourt RC, Jeziorowski A, Kaimoto CL, Mima WH, Saciloto A, Schultz JI, et al. Achados histopatológicos em mamoplastia redutora. Arquivos Catarinenses de Medicina. 2007;36(Suppl 1):59-60.

4. Matos JR, Cavalcante MM, Andrade SH, Pessoa SG. Achados histopatológicos de produtos de ressecção em mamaplastias redutoras. Rev Bras Cir Plást. 2011; 26(1):70-3.

5. Barros AR. Avaliação do estudo anatomopatológico em mamoplastia redutora [monografia]. Salvador: Universidade Federal da Bahia; 2013.

6. Keshtgar M, Jahromi AH, Davidson T, Escobar P, Mallucci P, Mosahebi A, et al. Tissue screening after breast reduction. BMJ. 2009;338:b630. DOI: 10.1136/bmj.b630

7. Sugita DH. Estudos histopatológicos de mamoplastias redutoras em hospital universitário. Análise de 10 anos [dissertação]. Uberlândia: Universidade Federal de Uberlândia; 2014.

8. Souza LH, Segundo SW, Dalul DB, Morais CM, Antunes DE, Pirani F, et al. Estudo histopatológico de 1.018 peças cirúrgicas de mamaplastia redutora. Rev Bras Cir Plást. 2005;20(3):173-5.

9. Celik B, Senen Demiroz D, Yaz M, Muslu U. Radiologically innocuous breast reduction specimes. Shoud we send them to pathology lab anyway? G Chir. 2013;34(11-12):302-6.

10. Jansen DA, Murphy MB, Kind GM, Sands KM. Breast cancer in reduction mammoplasty: case reports and a survey of plastic surgeons. Plastic and Reconstructive Surgery. 1998;101(2):361-4.

11. Desouki MM, Li Z, Hameed O, Fadare O, Zhao C. Incidental atypical proliferative lesions in reduction mammoplasty specimens: analysis of 2498 cases from 2 tertiary women's health centers. Hum Pathol. 2013;44(9):1877-81. DOI: 10.1016/j.humpath.2013.02.015

12. Hassan FE, Pacifico MD. Should we be analysing breast reduction specimens. A systematic analysis of over 1,000 consecutive cases. Aesthetic Plast Surg. 2012;36(5):1105-13.

SURGICAL TREATMENT OF BREAST CANCER: DATA FROM A RENOWNED INSTITUTION IN THE BRAZILIAN NORTHEAST

Tratamento cirúrgico do câncer de mama: dados de uma instituição de referência do nordeste brasileiro

Cibele Vasconcelos de Oliveira[1]*, Francisco Pimentel Cavalcante[1], Rafael Valente Batista[2],
José Carlos Lucena de Aguiar Ferreira[2], Olívio Feitosa Costa Neto[2], Marcos Venício Alves Lima[1,2]

ABSTRACT

Introduction: Worldwide, breast cancer is the neoplasia that most affects women, after skin cancer, and accounts for 25% of new cases each year. Over the past 40 years, the survival rate has been increasing in developed countries — currently, it is 85% in 5 years —, while in developing countries it remains between 50 and 60%. As such, routine use of mammography throughout the world is considerably important. **Objectives:** To describe demographic and pathological characteristics in addition to the surgical approach of patients with invasive breast carcinoma in a renowned institution. **Methods:** A cross-sectional, descriptive study using secondary data obtained from medical records of breast cancer patients operated on at the Cancer Institute of Ceará (ICC), from 2002 to 2012. Data were analyzed using Epi Info 7.0 software. **Results:** The study population included 746 patients with primary breast tumors, of which 626 (84%) were invasive. Within the invasive breast tumors, the majority (554 – 88.49%) were of the invasive ductal carcinoma (IDC) type. Concerning stages, 351 cases (56.07%) were stage II. The average age of patients was 41 to 50 years old, and T2 tumors measured approximately 2 to 5 cm. The most frequent surgery was a quadrantectomy. A sentinel lymph node biopsy (SNB) was performed in 368 patients (58.78%). **Conclusion:** Our casuistry provides important information with regard to the profile of patients surgically treated at a renowned public institution in the Brazilian Northeast. Diagnosing the disease at an advanced stage still occurs at this institution, which results in high rates of mastectomy. Thus, better results tend to be obtained as better screening proposals are provided.

KEYWORDS: Sentinel lymph node biopsy; carcinoma, ductal, breast; breast neoplasms.

RESUMO

Introdução: O câncer de mama é a neoplasia que mais acomete mulheres em todo o mundo após o câncer de pele, representando 25% dos casos novos a cada ano. Nos últimos 40 anos, a sobrevida vem aumentando nos países desenvolvidos — atualmente, é de 85% em 5 anos —, enquanto nos países em desenvolvimento permanece entre 50 e 60%, tendo o uso rotineiro da mamografia considerável importância em todo o mundo. **Objetivos:** Descrever as características demográficas, patológicas e as abordagens cirúrgicas de pacientes com carcinoma invasivo da mama em uma instituição de referência. **Métodos:** Estudo transversal e descritivo, utilizando dados secundários obtidos nos prontuários médicos de pacientes com câncer de mama operadas no Instituto do Câncer do Ceará (ICC), entre os anos de 2002 e 2012. Os dados foram analisados por meio do *software* Epi Info 7.0. **Resultados:** A população de estudo correspondeu a 746 pacientes com tumores primários de mama, dos quais 626 (84%) apresentavam-se como invasivos, sendo a maioria (554 – 88,49%) do tipo carcinoma ductal invasivo (CDI). No que diz respeito ao estádio, 351 casos (56,07%) eram II. Prevaleceu a faixa etária de 41 a 50 anos, e os tumores T2 mediam aproximadamente 2 a 5 cm. A cirurgia mais frequente foi a quadrantectomia; e a biópsia do linfonodo sentinela (BLS) foi realizada em 368 pacientes (58,78%). **Conclusão:** Nossa casuística fornece informações importantes sobre o perfil de pacientes portadoras de tumor invasivo da mama tratadas cirurgicamente em uma instituição filantrópica do Nordeste brasileiro, referência no tratamento do câncer. O estadiamento avançado ao diagnóstico ainda é presente nessa instituição, o que determina elevadas taxas de mastectomia. Assim, melhores resultados tendem a ser obtidos à medida que são apresentadas melhores propostas de rastreio de massa.

PALAVRAS-CHAVE: Biópsia de linfonodo sentinela; carcinoma ductal de mama; neoplasias da mama.

INTRODUCTION

Worldwide, breast cancer is the neoplasia that most affects women after skin cancer, and accounts for 25% of new cases each year. According to the Brazilian Cancer Institute (*Instituto Nacional do Câncer*—INCA), about 57,960 new cases are expected in 2017. There is a death estimate of 14,388, of which 181 are men and 14,206 are women (2013-SIM). In Ceará, 2,160 new cases are expected and, in Fortaleza, 860 cases are expected for the same period[1].

Over the past 40 years, survival rates have been increasing in developed countries — currently, it is 85% in 5 years —, while in developing countries it remains between 50 and 60%. This difference can be explained by the easy access to mammographic screening in the first world[2], which leads to the diagnosis of minor tumors[3] and in turn, to advancements in cancer treatment[4].

The routine use of mammography has spread throughout the world, leading to the early detection of breast cancer. However, much is still being discussed about the ideal age for beginning the screening, as well as the appropriate periodicity[5]. The Brazilian Society of Mastology recommends the introduction of screening at the age of 40, since a considerable number of women get cancer under the age of 50[1], obeying the annual periodicity.

The advancements in treatment also had an important impact on patient survival. The advent of modern adjuvant therapies, including chemotherapy, hormone therapy and target therapies, as well as the improvement of radiotherapy techniques, have made it possible to reduce surgery with the introduction of conservative techniques and a sentinel lymph node biopsy (SLNB), without harming oncological safety and with a paradoxical decrease in loco-regional recurrence rates[6-12].

In the state of Ceará, patients who require care in mastology have few units to rely on, both in primary and tertiary care. In this last category, there is the Cancer Institute of Ceará (*Instituto do Câncer do Ceará* – ICC), one of the few and the largest High Complexity Oncology Centers (*Centro de Alta Complexidade em Oncologia* – CACON) in the state.

Breast cancer has thus become the aim of this study, precisely because it represents a public health problem. Due to data limitations in the Brazilian Northeast, we developed this study with the goal of enabling future changes in public health policies associated with oncology to be executed on a scientific basis, avoiding empiricism in health decision-making in the region.

METHOD

This is a cross-sectional and descriptive study, based on secondary data obtained from the review of medical records of breast cancer patients undergoing surgical treatment at the ICC between 2002 and 2012. Regarding eligibility, an intentional sample was performed from the study population, whose inclusion criteria were: female patients with a previous diagnosis of invasive breast carcinoma obtained through core biopsy or surgical biopsy, and who had undergone surgical treatment. Patients with intraductal neoplasms, non-epithelial lineage tumors (sarcomas, lymphomas and phyllodes tumors) or with insufficient information in the medical records were excluded from the analysis. Data were tabulated and statistically treated using Epi Info 7.0 software. This study was approved by the Research Ethics Committee of ICC, under protocol no. 61,473 on July 26, 2012.

RESULTS

The study population included 746 patients with primary breast tumors, of which 106 presented ductal carcinoma in situ (DCIS) as an initial histopathological type, while 626 were classified as invasive tumors (Table 1). The remaining 14 patients were identified with sarcomas (4), phyllodes tumors (8) and lobular carcinomas in situ (2).

Of the 626 invasive tumors, 554 (88.49%) had invasive carcinoma of no special type (not otherwise specified – NOS) as a histopathological diagnosis; 35 (5.60%), invasive lobular carcinoma; 17 (2.72%), papillary carcinoma; 6 (0.95%), medullary carcinoma; 4 (0.64%), tubular carcinoma; 4 (0.64%), cribriform carcinoma; 3 (0.48%), metaplastic carcinoma; and 3 (0.48%), Paget's disease.

In relation to pathological staging (PS), stage I was found in 132 cases (21.08%); stage II in 351 (56.07%); stage III in 88 (14.05%); and stage IV in 8 (1.28%).

Regarding the age profile, the highest percentage was found between 41 and 70 years of age, distributed as follows: 9 (1.43%) under the age of 30; 53 (8.46%) between 31 and 40; 161 (25.71%) between 41 and 50; 145 (23.18%) between 51 and

Table 1. Distribution of the absolute and relative frequencies of histological types of invasive breast tumors operated on at the Ceará Cancer Institute between 2002 and 2012.

Histological type	N	Variation (%)
Invasive carcinoma (no special type)	554	88.49
Invasive lobular carcinoma	35	5.60
Papillary carcinoma	17	2.72
Medullary carcinoma	6	0.95
Cribriform carcinoma	4	0.64
Metaplastic carcinoma	3	0.48
Paget's disease	3	0.48

60; 168 (26.85%) between 61 and 70; and 90 (14.37%) older than 70 years old.

Regarding the size of the tumors, the majority of patients, at the first visit, had measurements between 2 and 5 cm. After stratification of the sizes, 162 (25.87%) showed a tumor smaller than 2 cm; 389 (62.14%) between 2 and 5 cm; and 64 (10.22%) larger than 5 cm.

Regarding surgery (Table 2), 278 (44.4%) were quadrantectomies; 92 (14.69%) were single mastectomies; 251 (40.09%) were modified radical mastectomies; 3 (0.47%) were Halsted radical mastectomies; and 2 (0.35%) were skin-sparing mastectomies with a conservation of the Nipple–Areola Complex (NAC). SLNB was performed in 368 (58.78%) cases. Among the SLNB patients, 100 (27.17%) had lymph nodes that were compromised by neoplasia, after having been submitted to axillary emptying (AE). Of these, 44 (44.0%) had additional lymph node disease, while 56 (56.0%) had disease-free axilla after AE.

DISCUSSION

With the evolution in diagnostic methods and comprehensive screening, breast cancer has been increasingly diagnosed in its early stages. There is, however, a controversy about the ideal age for the start of mammographic screening. In the study population, a considerable number of patients (35.6%) had a cancer diagnosis under the age of 50, which is in line with other studies[13,14]. For this reason, mammography screening in women over the age of 40 has been a subject of debate[5,13,14].

Late diagnosis is still a problem in our country. In this casuistry, stages II and III predominated (70.12%), while stage I accounted for 21.08%, suggesting that early detection has not yet fully achieved its goals. Other reviews showed a similar scenario, with a prevalence of later diagnosis. The study by Cintra et al.[15], for example, shows a prevalence of 86% for stages II and III. According to Abreu and Koifman[16], stages III and IV were the types most often found in public institutions for the treatment of breast cancer.

Table 2. Distribution of the absolute and relative frequencies of surgeries performed on patients with invasive breast tumors at the Ceará Cancer Institute between 2002 and 2012.

Type of surgery	N	Variation (%)
Quadrantectomy	278	44.40
Simple mastectomy	92	14.69
Radical modified mastectomy	251	40.09
Halsted radical mastectomy	3	0.47
Skin-sparing mastectomy with conservation of the Nipple–Areola Complex	2	0.35

In histology, there was a predominance of invasive carcinoma NOS (88.49%). The size of the tumors was concentrated in values between 2 and 5 cm (62.14%), while 25.87% were smaller than 2 cm. There are, however, regional differences in staging: in more developed regions, there are a larger number of early stages than those observed in this analysis, while less developed regions experience higher rates of locally advanced tumors[13,17]. Identifying these discrepancies can contribute to the improvement of tracking policies by region.

There was a predominance of mastectomies (55.6%) in their various forms when compared to conservative surgeries (44.4%) in the procedures performed, which is a possible reflection of the staging.

The radicalness of axillary surgery has also been decreasing over the years, with a reduction of inherent complications, especially due to early diagnosis and the advent of the sentinel lymph node (SLN)[8,9,11,18]. Although it cannot be denied that modified radical mastectomy is in decline, it is still very prevalent in underdeveloped regions, as demonstrated in this study. On the other hand, skin-sparing mastectomy with conservation of the Nipple–Areola Complex, at the time of development of this study (2002 to 2012), was reflected in rare patients.

SLNB was performed in 58.2% of the patients, while the others underwent axillary dissection. Of those who underwent SLNB, 100 (27.1%) showed positive SLN. Thus, more than two-thirds of the patients did not require AE and were spared the inherent morbidity of this procedure[18].

CONCLUSION

Our casuistry provides important information about the profile of patients surgically treated in a renowned philanthropic institution in the Brazilian Northeast. Our results, when compared to those obtained in other regions of Brazil, also show a tendency of the hospitals to perform less extensive procedures, either with regard to the surgical treatment of the primary tumor or with regard to the axillary approach, which may demonstrate a reduction in the number of patients with advanced stages of cancer. However, we cannot rule out that this phenomenon is the result of paradigm changes in the treatment of breast cancer.

Thus, we believe that actions in primary health care and the improvement of mass screening, in conjunction with improvements in surgical techniques and adjuvant treatments, will increase the rates of control of the disease, as well as reduce morbidity and mortality, and reduce the financial cost of treatment. This is fundamental, especially in regions that lack human capital, technological aids and financial resources for health services.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de Prevenção e Vigilância de Câncer. Estimativa 2016: Incidência de câncer no Brasil. Rio de Janeiro: INCA; 2015.

2. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. Lancet. 2000 May 20;355(9217):1822.

3. Coburn NG, Chung MA, Fulton J, Cady B. Decreased breast cancer tumor size, stage, and mortality in Rhode Island: an example of a well-screened population. Cancer Control. 2004 Jul-Aug;11(4):222-30.

4. Nyström L, Bjurstam N, Jonsson H, Zackrisson S, Frisell J. Reduced breast cancer mortality after 20 + years of follow-up in the Swedish randomized controlled mammography trials in Malmö, Stockholm, and Göteborg. J Med Screen. 2017 Mar;24(1):34-42.

5. Gebrim LH, Quadros LGA. Rastreamento do câncer de mama no Brasil. Rev Bras Ginecol Obstet. 2006 June;28(6):319-23.

6. Fisher B, Montague E, Redmond C, Deutsch M, Brown GR, Zauber A, et al. Findings from NSABP Protocol No. B-04-comparison of radical mastectomy with alternative treatments for primary breast cancer. I. Radiation compliance and its relation to treatment outcome. Cancer. 1980 Jul 1;46(1):1-13.

7. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med. 1995 Nov 30;333(22):1456-61.

8. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010 Oct;11(10):927-33.

9. Wilke LG, McCall LM, Posther KE, Whitworth PW, Reintgen DS, Leitch AM, et al. Surgical complications associated with sentinel lymph node biopsy: results from a prospective international cooperative group trial. Ann Surg Oncol. 2006 Apr;13(4):491-500.

10. Morrow M, Harris JR, Schnitt SJ. Surgical Margins in Lumpectomy for Breast Cancer — Bigger Is Not Better. N Engl J Med. 2012 Jul 5;367(1):79-82.

11. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011 Feb 9;305(6):569-75.

12. Freitas-Junior R, Siqueira LB, Carrijo ENA, Lacerda RP, Paulinelli RR, Rahal RMS, et al. Variação temporal do tratamento cirúrgico do câncer de mama em um hospital universitário na região Centro-Oeste do Brasil. Rev Col Bras Cir. 2013 June;40(3).

13. Haddad CF. Características clínico-patológicas e estadiamento ao diagnóstico de pacientes com câncer de mama em um centro de saúde do interior de Minas Gerais. Rev Bras Mastol. 2014;24(4):103-8.

14. Nunes BA, Siqueira SL, Pereira SM, Pacheco TJ, Pessanha TO, Mendonça SB. Perfil epidemiológico dos pacientes diagnosticados com câncer de mama em Campo dos Goytacazes. Rev Bras Mastol. 2012;22(4):117-23.

15. Cintra JRD, Guerra MR, Teixeira MTB. Sobrevida específica de pacientes com câncer de mama não-metastático submetidas à quimioterapia adjuvante. Rev Assoc Med Bras. 2008;54(4):339-46.

16. Abreu E, Koifman S. Fatores prognósticos no câncer da mama feminina. Rev Bras Cancerol. 2002;48:113-32.

17. Macchetti AH. Estadiamento do câncer de mama diagnosticado no sistema público de saúde de São Carlos. Medicina (Ribeirão Preto). 2007;40(3):394-402.

18. Piato JR, Carvalho FM, Costa PA, Barros ACSD. Biopsia do linfonodo sentinela. In: Barros ACSD, Buzaid AC. Câncer de mama: tratamento multidisciplinar. São Paulo: Dendrix; 2007. p.98-121.

IMPROVEMENT ASSESSMENT OF MASTOLOGIST IN THE BREAST ONCOPLASTIC AND RECONSTRUCTIVE SURGERY OF SANTA CASA DE BELO HORIZONTE, MG, BRAZIL

Avaliação do aprimoramento do mastologista em cirurgia oncoplástica e reconstrutiva da mama da Santa Casa de Belo Horizonte

Douglas de Miranda Pires[1], Carolina Lemos Baroncelli[2], Cicero de Andrade Urban[3],
Carolina Nazareth Valadares[1]*, Mariana dos Santos Nascimento[1], Izabel Aparecida Cunha Andrade[1]

ABSTRACT

Objective: This study aims to investigate the efficacy and improvement of knowledge acquired by breast cancer specialists in a postgraduate course of Oncoplastic Surgery conducted in Santa Casa de Belo Horizonte (SCBH). **Method:** For this evaluation, an exploratory qualitative study was carried out. It was supported by an online survey questionnaire sent to 36 breast cancer specialists, who had taken the course in the period from 2012 to 2014. The data were interpreted using statistical methods, as well as probabilistic sampling. **Results:** After the Oncoplastic Surgery course, almost all breast cancer specialists who had taken it demonstrated the ability to reconstruct the breasts of women who had undergone mastectomies with oncoplastic techniques. A large portion of the specialists was able to develop bilateral treatment with breast reduction, mastopexy and rebuild areolas and nipples, as well as immediately reconstruct the breast with expanders or prosthesis and contralateral symmetrization. A significant amount of professionals was able to perform breast reconstruction with autologous flaps. **Conclusion:** The course for the Professional Development of Breast Cancer Specialists sponsored by the Teaching and Research Institute of Santa Casa de Belo Horizonte was able to improve the skills of the professionals involved in the different breast remodeling and reconstruction techniques. This enables a paradigm shift in the treatment of cancer patients.

KEYWORDS: Breast Cancer; Breast reconstruction; Breast diseases.

RESUMO

Objetivo: Este trabalho objetiva investigar a eficácia e aprimoramento dos conhecimentos adquiridos por mastologistas no Curso de Pós-graduação de Oncoplastia Mamária da Santa Casa de Belo Horizonte (SCBH). **Método:** Para essa avaliação, realizou-se um estudo exploratório de natureza qualitativa. Como suporte, a aplicação de questionário de pesquisa, enviado *online* aos trinta e seis mastologistas que fizeram o Curso, no período de 2012 a 2014. Os dados foram interpretados por intermédio de métodos estatísticos, bem como por uma amostragem probabilística. **Resultados:** Após o Curso, quase a totalidade dos Mastologistas que se aprimoraram se mostram capazes de reconstruir a mama das mulheres mastectomizadas com técnicas oncoplásticas. Uma grande parcela tem condições de desenvolver tratamento bilateral com redução mamária, mastopexia e reconstruir aréolas e mamilos, e reconstruir de maneira imediata a mama, com expansores ou próteses e simetrização contralateral. Uma quantidade significativa dos profissionais é capaz de efetuar a reconstrução da mama com retalhos autólogos. **Conclusão:** O Curso promovido por esse Instituto de Ensino e Pesquisa foi capaz de aprimorar os profissionais envolvidos, nas diferentes técnicas de remodelamento e reconstrução mamária. Isso possibilita uma mudança de paradigma no tratamento da paciente oncológica.

PALAVRAS-CHAVE: Câncer de mama; Reconstrução da mama; Doenças da mama.

INTRODUCTION

According to the World Health Organization (WHO)[1], a high incidence of cancer has been caused by a rapid change in the lifestyle of people in developing countries, which increasingly resemble those of industrialized countries. The increase in smoking and obesity rates, as well as in life expectancy also contribute to an increase in the number of breast cancer cases.

In Brazil, the cancer problem has become relevant because of the disease's epidemiological profile, thus entering into the political and technical agendas of all governmental spheres. Knowledge about cancer permits the establishment of priorities and the allocation of resources towards a positive change in the Brazilian population.

Excluding non-melanoma skin cancer, breast cancer is the second most common type in the world and is the most common among women, accounting for 22% of new cases each year. The highest occurrence of the disease among Brazilian women occurs in the Southeast region, where there are 64.54 cases/100,000 women. In the Southern region — 64.3/100,000 women; Midwestern region — 37.68/100,000 women; Northeastern region — 30.11/100,000 women; and Northern region, with the lowest incidence, 16.62/100,000 women. This data reflects a more industrialized society that has increasing consumption of unhealthy food, obesity, stress, sedentary lifestyles, alcohol consumption and a higher parity rate, or at least the beginning of these indices[2].

Among the different situations and lesions, if mastectomy is required, the ideal solution is immediate breast reconstruction, since it can reduce the impact caused by this type of cancer. With the increase in overall survival of women with breast cancer, this alternative procedure is considered in such situations.

The evaluation of quality of life has become an increasingly used and valued parameter, and has guided the decisions of health professionals and patients with the most diverse diseases[3]. Aspects such as function, dysfunction, in addition to physical and emotional discomfort are relevant to the quality of life for a given function, population or symptom. Loss of the breast can cause devastating effects that include physical and psychic depreciation. Restorative surgery can increase the functional capacity and the psychological well-being of patients, especially with regard to self-esteem.

According to the Brazilian National Cancer Institute (*Instituto Nacional do Câncer*—INCA)[4], Law No. 12.802/2013 requires that the Public Health System (*Sistema Único de Saúde* — SUS) perform restorative surgery on women who have had their breast removed due to cancer, and who show favorable clinical conditions. Also, Data from the Public Health System Database (Datasus, 2013) show that less than 10% of Brazilian patients who have undergone a mastectomy have access to immediate breast reconstruction through SUS[4]. This means that an immense majority of these women continue to have asymmetries and important aesthetic defects. In the country, the rates of immediate reconstruction are very low, although there is specific legislation that provides for the possibility of this surgery.

The main reason for delayed reconstruction is the lack of trained professionals to perform this type of surgery[5].

Far from being a specialty or attribute, mammary oncoplasty is a set of surgical skills and techniques used for the purpose of providing patients with better aesthetic results without sacrificing oncological treatment (which must always come before aesthetics). It encompasses surgical techniques for breast reconstruction and remodeling that can be applied to both the cancerous and the contralateral breast[6]. Its use allows for a broad tumor approach, favors safe cancer margins, and can be an important tool in reducing the risks of compromised margins and reoperations[7]. The procedure is a technique to be learned, developed, elaborated on, and increasingly performed by breast cancer specialists in breast cancer treatments.

The purpose of the different Hands-on Breast Cancer Oncology courses, each of which has its own characteristics, is to improve the training of specialists so that they are more qualified. Their purpose is to guarantee comprehensive care in the treatment of this type of cancer, as well as to promote the importance of this reconstruction[8].

It is assumed that a portion of these professionals does not have the inclination or opportunity to learn breast reconstruction techniques, and practice patterns will depend on local circumstances and available opinions. The SBM's Oncoplastic and Reconstructive Surgery Commission (2013–2016 triennium) defined that a specific certification in the field of Mastology is not necessary, but recommends that professionals who are interested in this surgical approach, and who have not had the opportunity to perform a more specific training, seek training in breast reconstruction techniques[7].

This study aims to investigate the applicability of the systematization of the improvement of breast cancer specialists who took the course in the period from 2012 to 2014, in Santa Casa de Belo Horizonte (SCBH). The article tries to generate factors that allow for the constant evaluation of the course's curricular material, especially in its more technically related contents. Furthermore, it aims to subsidize the decision-making process for changes, especially with respect to special topics that propose an offering of relevant content for practical improvement[9].

Similar studies to this evaluation have already been published by other training centers in Mammary Oncology, such as Hospital Araújo Jorge in Goiânia and Hospital do Câncer de Barretos. Each of them points out the singularities and highlights of their courses and students[10].

METHODS AND MATERIALS

For this evaluation, an exploratory, qualitative study was carried out[11]. According to Minayo, the qualitative view is the "locus where conflicts and compromises, traditions and changes, are articulated, and where everything has meaning, or meanings,

since there is never anything human in meaning nor just one explanation for the phenomena they encompass"[11]. The qualitative analysis allows for the decoding of the content presented by the subjects of this study and translates their reality. According to Fontanella et al., "the testimonies of the subjects are understood as representing a segment of belonging"[12]. They go from "me" to "us".

In order to characterize the "life-rebuilding" activities of the women by the professionals who took the Oncology and Reconstructive Breast Surgery Improvement Course at SCBH, a quantitative data survey was chosen. The hypothesis here is not causal, but aims to verify if the perception and performance of professionals are in accordance with the reality investigated.

In this investigation, the research was conducted using a questionnaire survey with eleven multiple-choice questions. It was sent online to breast cancer specialists (thirty-six of them), who took the course in the mentioned period (Appendix 1). The aim was to identify their profile, how the practices are done in their different realities, and the possible shifts in paradigms in the treatment of cancer patients.

Multiple-choice questions have the following advantages: ease of application, processing and analysis, and quick response. They furthermore present little possibility of error. The disadvantages are that they require great care and preparation time to ensure that all response options are offered. If a major alternative option has not been previously included, strong biases may occur, even when the option for "other" and the question "which ones" are included. The respondent may be influenced by the options presented.

The questionnaire followed the prerogatives established in the study and had certain guiding principles from Moscarola[13] (Figure 1), in which the measurement of the variables describes the characteristics of the sample.

In spite of the fact that the survey was clearly defined for professionals and there was adequate time between questions and feedback, 16 of them did not respond to the questions (44.4%). This aspect was a limiting factor in the study.

Because it could affect the expected quality of the results, the possibility of developing a probabilistic (valid) sample, composed by the group of professionals that answered the survey,

was questioned. A valid sample is considered to be a representative subset of the target population.

DISCUSSION

For professionals who did not have specific training, the practical courses supported by SBM are an appropriate methodology to assist them in their practices.

The "Lato Sensu" Post-Graduate Course of Santa Casa de Belo Horizonte (SCBH) aims to "provide training and professional development in surgical procedures for breast remodeling after breast cancer surgery, techniques for breast reconstruction, corrective mastoplasty, and management of surgical intercurrences"[9].

The course began as a medical extension program that had practical training in the operating room and covered various surgical procedures related to this type of remodeling. The initiative was successful, and from 2012 until today, it has been constituted as a "lato sensu" program. Similarly to other different courses at this particular educational institution, it adopts "a differentiated didactic/pedagogical methodology in relation to the other available courses"[9].

In the training and professional development program organized by SCBH, in the period from 2012 to 2014, students had monthly classes with three teachers. Thirty-six doctors participated in the course, which made it possible to provide care for two hundred and ninety-three patients[9]. Some of them underwent surgical procedures more than once, as there were cases in which two or three surgeries were necessary to complete the treatment.

For doctors who participate in this type of training, the Brazilian Society of Mastology (SBM) requires that they received the title of "specialist" from the institution.

In 2012, for the training and excellence of the professionals, the activities were presented in six modules with a total of 144 hours. In the period between 2013 and 2014, the workload was increased to 240 hours in a total of 10 modules. They were distributed as follows:

1. Oncoplastic Breast Surgery (24 hours);
2. Corrective mastoplasty (24 hours);
3. Dermoglandular patchwork (24 hours);
4. Review of techniques: refinement and management of complications (24 hours);
5. Breast Implants (24 hours);
6. Myocutaneous flaps (24 hours);
7. Myocutaneous flaps (24 hours);
8. Review and improvement of procedures (24 hours);
9. Alternative techniques (24 hours);
10. Refinement and management of complications (24 hours)[9].

The course proposal for the years 2015 and 2016 consists of fifteen modules with a total of 540 hours. Similar to the courses offered in previous years, after completion of the professional

Points of interest:
- Identity — Who?
- Behavior — Does what?
- Reason — For what reason?
- Opinions/values — With what purpose?
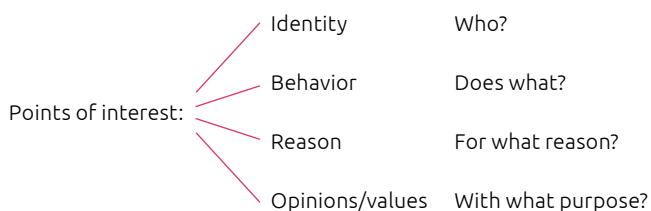
Source: Moscarola[13].

Figure 1. The questionnaire as a list.

development program, participants must be certified by the national SBM[9].

The reflections are defined from the understanding of the potential (practical efficiency) of the professional development for the breast cancer specialists in the period from 2012 to 2014 in SCBH. Based upon this premise, it was possible to establish the survey, which evaluates the course from the point of view of professionals before and after its completion. Research, as Minayo states, "is a way to understand something holistically, even freeing it from disciplinary ties[11]."

Similar to Mizukami et al.'s research on the integration of scientific-pedagogical and personal knowledge[14], it is understood that, from the analysis, the professionals specialized in this professional development can benefit from reflecting on its practices, learning to systematize their specific knowledge and become aware of theories that justify their decisions and attitudes in the real context of work. This knowledge is built in action and it explains "secret and sacred stories"[14] that reveal beliefs and hypotheses that guide their professional practices and question their convictions, allowing them to share their knowledge among peers. In the sense that the authors (2002) give to them, sacred histories are constituted of personal perceptions of practice and are related to theories shared by peers. As for the secrets, they correspond to the daily practices of the professionals. They are experienced without external judgment and are apparently disconnected from theoretical references. Through the revelation of the secret stories, tactical knowledge-oriented practices can be recognized (2002)[14].

According to experts at the SBM, immediate breast reconstruction procedure improves the oncological and aesthetic results of breast cancer[7]. Although there is consensus among the experts that there is no need for specific training for professionals to carry out these procedures, they consider the training of breast cancer specialists on all reconstructive techniques to be quite important[7].

On the one hand, there is the perception that, every year, the incidence rate of breast cancer diagnoses increases. On the other hand, there is the possibility that improved surgical techniques can carry out the treatment more safely and with minimal aesthetic and functional damages[15]. Thus, a model that can be followed is urgently needed, so that cancer treatment safety is aligned with aesthetic and functional results, and so that these women can have a better quality of life. "Surgeons must be attentive, trained, and dedicated to perfection[8]."

The training in Oncoplastic Surgery is established at the following competence levels:

- Level I: Unilateral treatment with tissue mobilization;
- Level II: Bilateral treatment with breast reduction, mastopexy and reconstruction of the areola and nipple;
- Level III: Immediate reconstruction of the breast, with expanders or prosthesis and contralateral symmetrization;

- Level IV: Reconstruction with autologous flaps[16].

The professional development allows for a paradigm shift in the treatment of cancer patients. Also, when exploring how surgical breast reconstruction activities develop after the course, breast cancer is part of the professionals' responsibility toward social health.

It is believed that a more intense training of professionals in this type of procedure is necessary, both for the graduates of the residency programs in addition to those that have not yet had the possibility to develop the techniques in a systematic training. Continued improvement in this area may result in safer reconstructive activities that provide patients with cancer treatment associated with breast reconstruction — even in more complex cases, with recto-abdominal or large-dorsal flaps, for example.

Similarly to the specialists[5], it is expected that each of the practitioners who have completed the SCBH course become a multiplier of the improved knowledge. This, ideally, will generate further improvement both in breast reconstruction rates in Brazil and in the quality of life of patients with breast cancer.

RESULTS

Data were collected from January to May of 2016 from a total of twenty respondents. This data is presented in Appendix 2.

The answers obtained from the survey were analyzed and placed in graphs to better visualize them. Qualitative variables resulted in attributes or qualities (gender, work motivation, concept learning, for example). The quantitative variables resulted in numbers of certain scales.

The proposed classification of the competence levels[16] guide the breast reconstruction activities of the professionals investigated. Before taking the course at SCBH:

- 76.5% performed Level I techniques;
- 5.9% performed Level II techniques;
- 23.5% performed Level III techniques;
- 11.8% performed Level IV techniques.

After the course, there was an increase in competence in the breast reconstructive activities of these professionals, as follows:

- 95% were now able to perform Level I techniques;
- 75% were now able to perform Level II techniques;
- 80% were now able to perform Level III techniques;
- 40% were now able to perform Level IV techniques.

Consequently, there is the possibility that the final result of the survey can act as a guide for the institution and for future professionals, who will benefit from the information regarding the professional and scientific potential of Oncoplastic Surgery Professional Development and Reconstructive Breast Care.

CONCLUSION

The purpose of this study is to investigate the applicability of the systematization for the professional development of breast cancer specialists who completed the SCBH Course in the period from 2012 to 2014.

Based on the results obtained, it can be concluded that the course for the Professional Development of Breast Cancer Specialists in Oncoplastic and Reconstructive Breast Surgery promoted by SCBH is a very valid way for the professionals being specialized to benefit in the reflection of their practices, They learn to systematize their knowledge and additionally become aware of the theories that justify their decisions and attitudes in the real context of work. Moreover, they rebuild the lives of women who have become fragile with the disease, explain and rebuild the secret and sacred stories of both professionals and patients, and, finally, share knowledge and practices for the psychological well-being and a better quality of life for those involved.

REFERENCES

1. Organização Mundial da Saúde. [Internet]. [cited on Feb. 2015]. Available from: http://www.who.int/eportuguese/publications/pt

2. Sociedade Brasileira de Mastologia. [Internet]. [cited on Apr. 2015]. Available from: http://www.sbmastologia.com.br/index/index.php/rastreamento-e-diagnostico/60-estatisticas-sobre-cancer-de-mama-no-brasil

3. Ferraz MB. Tradução para o português e validação do questionário para avaliar a capacidade funcional "Stanford Health assessment questionnaire" [thesis]. São Paulo: Escola Paulista de Medicina, Universidade Federal de São Paulo; 1990.

4. Brasil. Senado. Lei obriga reconstrução de mama [Internet]. 2013 [cited on 15 May. 2016]. Available from: http://www12.senado.gov.br/jornal/edicoes/2013/05/07/lei-obriga-reconstrucao-de-mama

5. Instituto Nacional de Câncer José Alencar Gomes da Silva. Novos construtores de autoestima. Rev Rede Câncer [Internet]. 2014 [cited on Nov. 2015];27:29-31. Available from: http://www2.inca.gov.br/wps/wcm/connect/revistaredecancer/site/home/n27/revista_27

6. Resende M de A. Reflexões oncoplásticas aos mastologistas brasileiros. Rev Bras Mastologia. 2012;22(11):1-2.

7. Urban C, Freitas Jr. R, Zucca-Matthes G, Blazús JVN, Brenelli FP, Pires DM, et al. Cirurgia Oncoplástica e Reconstrutiva da Mama: Reunião de Consenso da Sociedade Brasileira de Mastologia. Rev Bras Mastologia. 2015;25(4):118-24. DOI: 10.5327/Z201500040002RBM

8. Hartt V. Em defesa da Oncoplástica [Internet]. 2016 [cited on May 2016]. Available from: http://www.onconews.com.br/site/noticias/noticias/entrevistas/612-em-defesa-da-oncopl%C3%A1stica.html

9. Santa Casa de Misericórdia de Belo Horizonte [Internet]. [cited on May 2015]. Available from: http://www.santacasabh.org.br/inscricoes/registros/index/cirurgia-oncoplastica-da-mama-hands-on-1.html#.VkubI_mrSUk

10. Paulinelli RR, Ribeiro LFJ, Moura Filho JWCM, Urban CA, Freitas Jr. R. Resultados do Programa de Educação Continuada em Oncoplastia e Reconstrução Mamária da Sociedade Brasileira de Mastologia no Hospital Araújo Jorge em Goiânia. Rev Bras Mastologia [Internet]. 2016 [cited on Nov. 2015];26(4):146-52. Available from: http://www.rbmastologia.com.br/wp-content/uploads/2016/11/MAS-v26n4_146-152.pdf

    DOI: 10.5327/Z201600040002RBM

11. Minayo MCS. O desafio do conhecimento científico: pesquisa qualitativa em saúde. 2ª ed. São Paulo: Hucitec-Abrasco; 1994.

12. Fontanella BJB, Ricas J, Turato ER. Amostragem por saturação em pesquisas qualitativas em saúde: contribuições teóricas. Cad Saúde Pública. 2008;24(1):17-27. http://dx.doi.org/10.1590/S0102-311X2008000100003

13. Moscarola J. Enquêtes et analyse de données. Paris: Vuibert; 1990.

14. Instituto Nacional do Câncer José Alencar Gomes da Silva [Internet]. [cited on Nov. 2015]. Available from: http://www2.inca.gov.br/wps/wcm/connect/tiposdecancer/site/home/mama/cancer_mama

14. Mizukami MGN, Reali AMMR, Reyes CR, Martucci EM, Lima EF, Trancredi RMSP, et al. Escola e aprendizagem da docência: processos de investigação e formação. São Carlos: EdUFSCar; 2002.

15. Instituto Nacional do Câncer José Alencar Gomes da Silva. Mama [Internet]. [cited on Apr. 2015]. Available from: http://www2.inca.gov.br/wps/wcm/connect/tiposdecancer/site/home/mama/cancer_mama

16. Urban C, Rjetiens M, Hurley II J. Oncoplastic and reconstructive surgery: qualifications, limits and mentoring. In: Urban C, Rjetiens M, Eds.. Oncoplastic and reconstructive breast surgery. Italia: Springer-Verlag; 2013. p. 44.

Appendix 1. Questions for professionals.

Age:
Sex: ☐ Female
☐ Male

City and State of professional practice:

1. Your certification by specialty is:
Specialist Title (T), Residence (R) and/or Specialization (S)

	T	R	S
General Surgery	☐	☐	☐
Oncology Surgery	☐	☐	☐
Plastic Surgery	☐	☐	☐
Gynecology and Obstetrics	☐	☐	☐
Mastology	☐	☐	☐

2. In what specialties do you perform?
☐ General Surgery
☐ Oncology Surgery
☐ Plastic Surgery
☐ Gynecology and Obstetrics
☐ Mastology

3. Academic background, scientific production and qualifications:
☐ Master's degree
☐ Doctorate degree
☐ Professor
☐ Preceptor

4. How many new cases of cancer are treated annually by you in your service?
☐ Below 50
☐ From 50 to 100
☐ From 100 to 200
☐ Above 200

5. Who performs breast reconstructions in your service?
☐ Mastologist.
☐ Mastologist and plastic surgeon.
☐ Plastic surgeon.
☐ We do not perform breast reconstructions.

6. Regarding immediate reconstructions in patients who undergo mastectomy in your service, identify the alternative that most adequately corresponds to your reality:
☐ Less than 10% of the mastectomized patients undergo immediate reconstruction.
☐ 10 to 20% of the mastectomized patients undergo immediate reconstruction.
☐ 20 to 50% of the mastectomized patients undergo immediate reconstruction.
☐ More than 50% of the mastectomized patients undergo immediate reconstruction.

7. In relation to your training in Oncoplastic and Reconstructive Surgery, identify the alternative that most adequately corresponds to your reality:
☐ I do not perform any form of oncoplastic and breast reconstruction surgery.
☐ I perform oncoplastic and breast reconstruction surgery together with another mastologist.
☐ I perform oncoplastic and breast reconstruction surgery together with a plastic surgeon.
☐ I refer the patient to oncoplastic and breast reconstruction surgery at a later time.
☐ I perform oncoplastic and breast reconstruction surgery in all cases.
☐ I perform oncoplastic and breast reconstruction surgery in some cases.

8. How are immediate post-mastectomy reconstructions performed in your service?
☐ Predominantly with expanders and prostheses.
☐ Predominantly with pedicled autologous flaps.
☐ Predominantly with microsurgical flaps.

9. Regarding aesthetic and functional breast surgeries in non-cancer patients, identify the alternative that most adequately corresponds to your reality:
☐ I perform reduction surgeries, mastopexy and augmentation mammoplasty.
☐ I do not perform such surgeries.

Appendix 1. Continuation.

10. At the beginning of the course, what was your reality?
☐ Able to perform partial reconstructions with oncoplastic techniques.
☐ Able to perform reconstructions with expanders and prostheses.
☐ Able to perform reconstructions with latissimus dorsi muscle.
☐ Able to perform reconstructions with TRAM.
☐ Able to perform breast reduction surgeries.
☐ Able to perform breast augmentation surgeries.

11. At the end of this course, what is your reality?
☐ I am able to perform partial reconstructions with oncoplastic techniques.
☐ I am able to perform reconstructions with expanders and prostheses.
☐ I am able to perform reconstructions with latissimus dorsi muscle.
☐ I am able to perform reconstructions with TRAM.
☐ I am able to perform reductive mastoplasty surgeries.
☐ I am able to perform augmentative mastoplasty surgeries.

Appendix 2. Responses from professionals.

Professionals who answered the questions: 20
Age: between 33 and 73.
Sex: 7 women (35%) and 13 men (65%)
States of practice: MA, CE, PI, PE, MG, PR, SC, TO, GO and MT

Question 1 – Certification by field
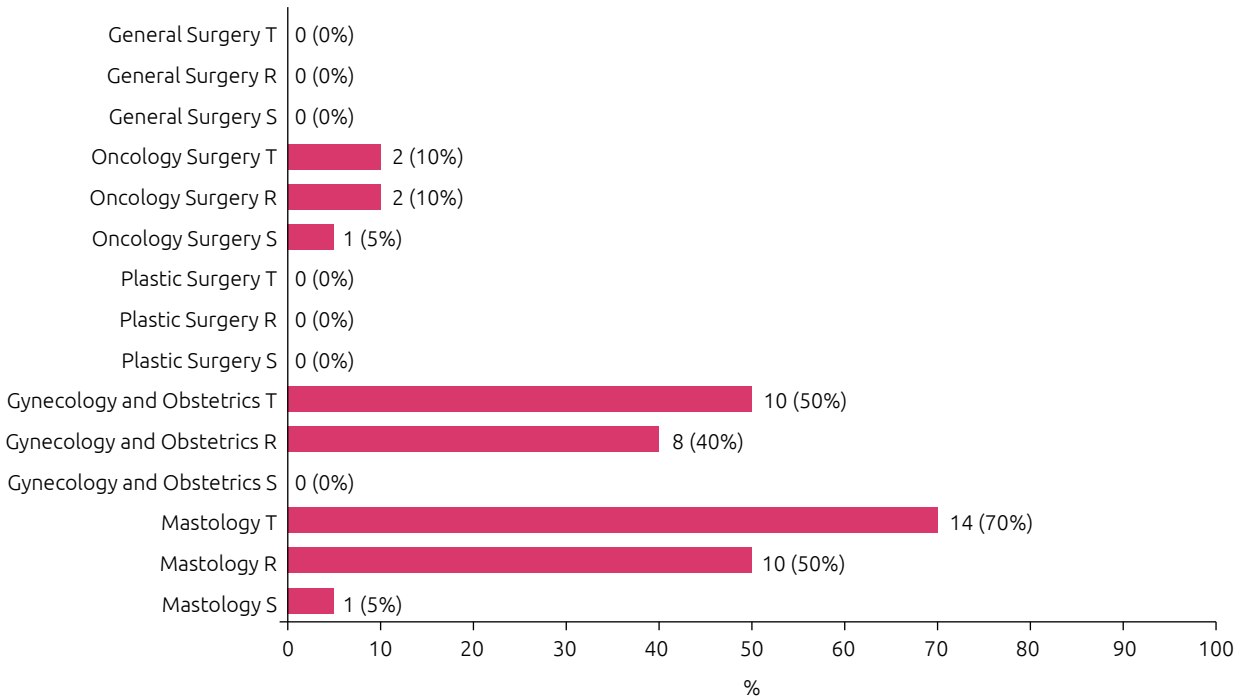
Question 2 – Field of practice of the professionals
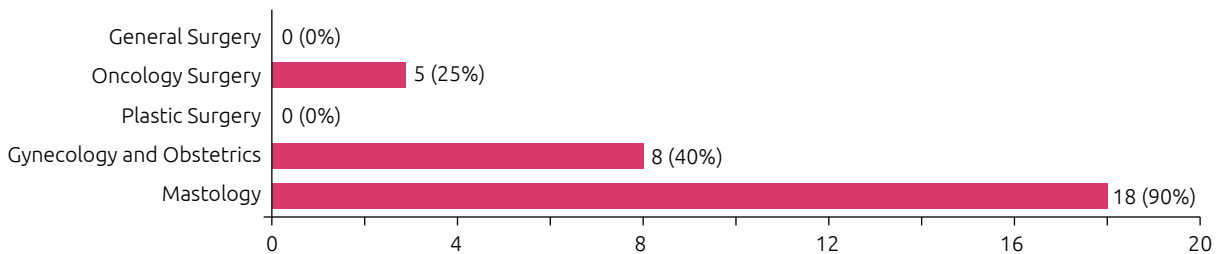
Appendix 2. Continuation.

Question 3 – Academic background, scientific production, qualifications

Degree	Value
Master's degree	7 (35%)
Doctorate degree	5 (25%)
Professor	6 (30%)
Preceptor	10 (50%)
None of the above	5 (25%)
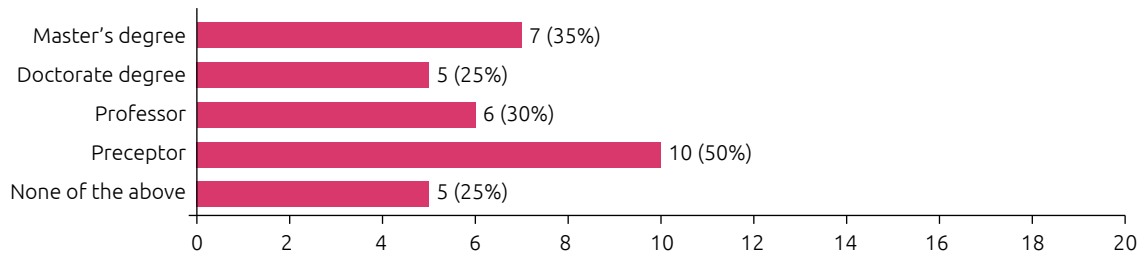
Question 4 – New cases of cancer treated annually by the professional in the service

Category	Value
Below 50	6 (30%)
From 50 to 100	10 (50%)
From 100 to 200	3 (15%)
Above 200	1 (5%)
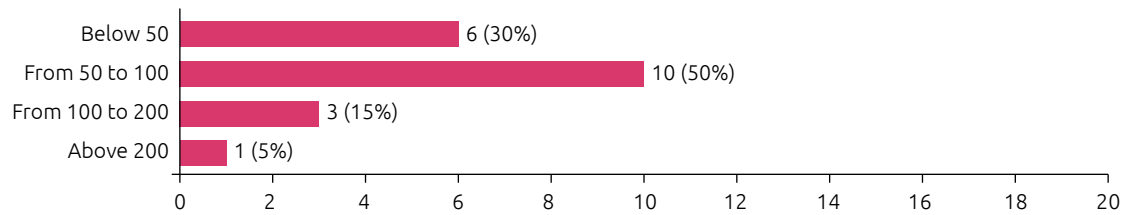
Question 5 – Who performs breast reconstructions in the respondent's service?

- Mastologist (10) — 50%
- Mastologist and Plastic Surgery (8) — 40%
- Plastic Surgery (1) — 5%
- Does not perform breast reconstructions (1) — 5%
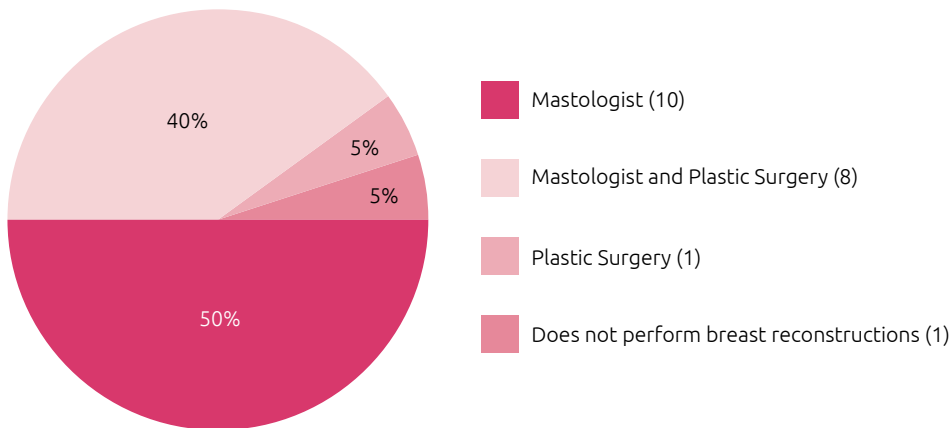
Question 6 – Regarding immediate reconstructions in patients who undergo mastectomy in your service, identify the alternative that most adequately corresponds to your reality:

- Less than 10% of the mastectomized patients undergo immediate reconstruction (4) — 20%
- 10 to 20% of the mastectomized patients undergo immediate reconstruction (1) — 5%
- 20 to 50% of the mastectomized patients undergo immediate reconstruction (3) — 15%
- More than 50% mastectomized patients undergo immediate reconstruction (12) — 60%
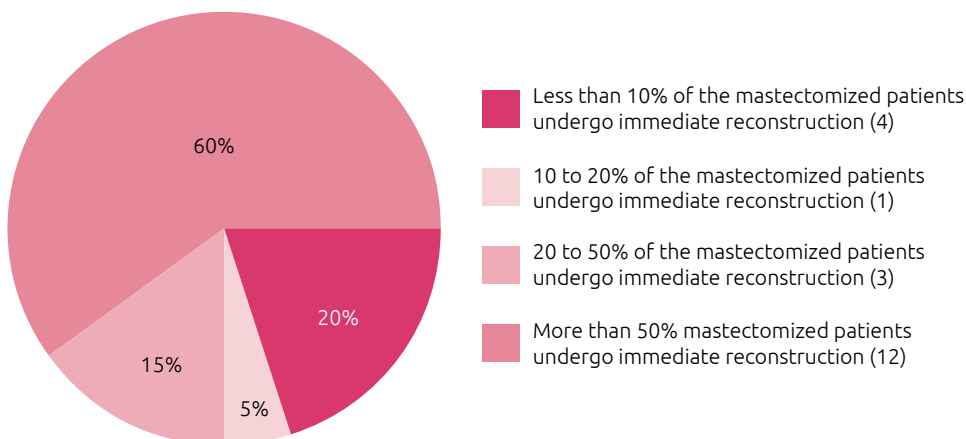
Appendix 2. Continuation.

Question 7 – In relation to your training in Oncoplastic and Reconstructive Surgery, identify the alternative that most adequately corresponds to your reality:

I do not perform any form of oncoplastic and breast reconstruction surgery — 1 (5%)

I perform oncoplastic and breast reconstruction surgery together with another mastologist — 7 (35%)

I perform oncoplastic and breast reconstruction surgery together with a plastic surgeon — 3 (15%)

I refer the patient to oncoplastic and breast reconstruction surgery at a later time — 0 (0%)

I perform oncoplastic and breast reconstruction surgery in all cases — 4 (20%)

I perform oncoplastic and breast reconstruction surgery in some cases — 10 (50%)

Question 8 – How are immediate post-mastectomy reconstructions performed in your service?

Predominantly with expanders and prostheses — 18 (90%)

Predominantly with pedicled autologous flaps — 2 (10%)

Predominantly with microsurgical flaps — 0 (0 %)
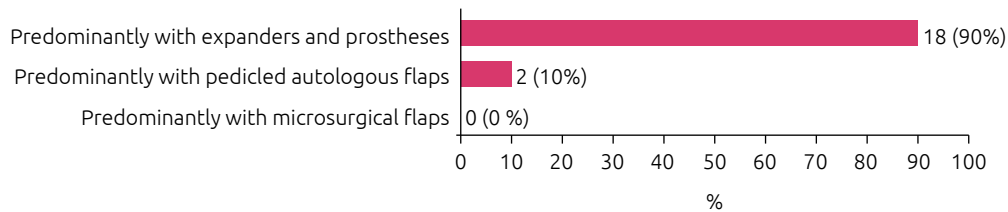
Question 9 – Regarding aesthetic and functional breast surgeries in non-cancer patients, identify the alternative that most adequately corresponds to your reality:

80%

20%

- I perform reduction surgeries, mastopexy and augmentation mammoplasty (4)
- I do not perform such surgeries (16)
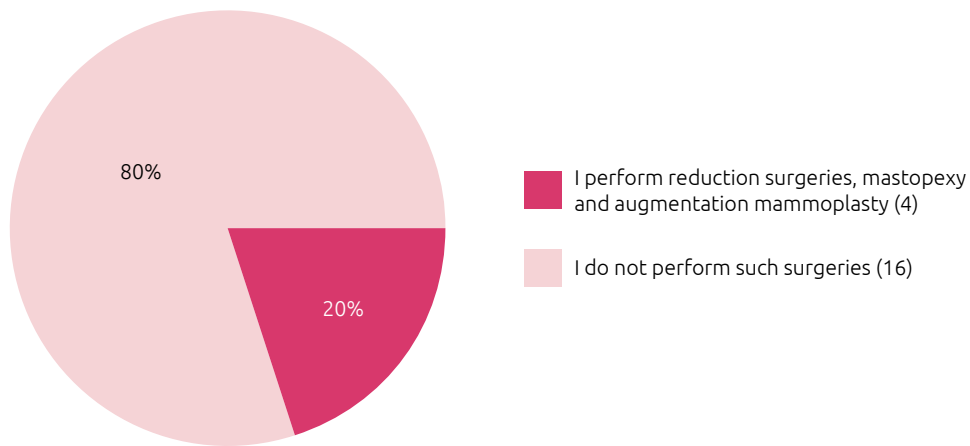
Question 10 – At the beginning of the course, the professionals were able to perform:

Partial reconstructions with oncoplastic techniques — 13 (76.5%)

Reconstructions with expanders and prostheses — 4 (23.5%)

Reconstructions with latissimus dorsi muscle — 2 (11.8%)

Reconstructions with TRAM — 1 (5.9%)

Breast reduction surgeries — 1 (5.9%)

Breast augmentation surgeries — 0 (0%)
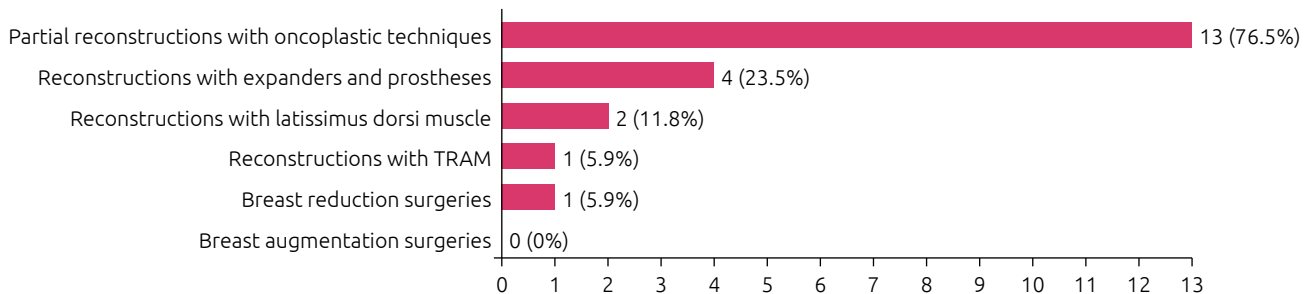
Appendix 2. Continuation.

Question 11 – At the end of this course, the reality of the professionals is:

Able to perform partial reconstructions with oncoplastic techniques	19 (95%)
Able to perform reconstructions with expanders and prostheses	16 (80%)
Able to perform reconstructions with latissimus dorsi muscle	8 (40%)
Able to perform reconstructions with TRAM	5 (25%)
Able to perform reductive mastoplasty surgeries	15 (75%)
Able to perform augmentative mastoplasty surgeries	13 (65%)

EPIDEMIOLOGICAL ANALYSIS AND INVESTIGATION OF +114G/T POLYMORPHISM IN THE GENE IL-2 IN PATIENTS WITH BREAST CANCER IN THE STATE OF MATO GROSSO

Análise epidemiológica e investigação do polimorfismo +114G/T no gene IL-2 em pacientes com câncer de mama no estado de Mato Grosso

Silvia Barassuol Sommavilla[1]*, Aguiar Farina[2], Danebe Fernandes de Araújo[3], Bianca Borsatto Galera[2]

ABSTRACT

Objective: This study aimed to determine the relationship between the rs2069763 polymorphism of the Interleukin-2 (IL-2) gene and the development of breast cancer (BC) in women in the state of Mato Grosso. **Methods:** This is an observational epidemiological study of case-control based on a bank of samples with 254 patients and 243 control women. The patients were subjected to anamnesis and collection of peripheral blood after their permission. The collecting of peripheral blood was carried out and was used for DNA extraction, followed by a genotyping process by Polymerase Chain Reaction-Restriction Fragment Length Polymorfism (PCR-RFLP) and polyacrylamide gel electrophoresis 8%. **Results:** The frequency of genotypes between cases and controls was 19.5% for the TT genotype; 44.2% and 32.1% for TG and GG, respectively. It was found, in samples of patients, a frequency of 14.9% for the TT genotype, 77.2% and 31.8% for TG and GG, respectively. In the controls, it was observed frequency of 24.1% for the TT genotype, 41.5% and 30.4% for TG and GG, respectively. **Conclusions:** The present study showed a higher incidence of polymorphism +114G/T in the control sample, suggesting a protective effect for the BC in the sample of women from Mato Grosso.

KEYWORDS: Breast Cancer; Genetic Polymorphism; Interleukin.

RESUMO

Objetivo: O presente estudo teve como objetivo verificar a relação existente entre o polimorfismo rs2069763 do gene interleucina-2 (IL-2) e o desenvolvimento do câncer de mama (CM) em mulheres do estado de Mato Grosso. **Métodos:** Trata-se de um estudo epidemiológico observacional do tipo caso controle tendo como base um banco de amostras com 254 pacientes casos e 243 mulheres controles. As pacientes foram submetidas à anamnese e à coleta de sangue periférico após terem autorizado os procedimentos. Procedeu-se a coleta de sangue periférico e este foi utilizado para a extração do DNA, seguido pelo processo de genotipagem por meio da técnica de *Polymerase Chain Reaction-Restriction Fragment Length Polymorfism* (PCR-RFLP – Reação em Cadeia da Polimerase-Polimorfismo no Comprimento de Fragmentos de Restrição) e eletroforese em gel de poliacrilamida 8%. **Resultados:** A frequência dos genótipos, entre casos e controles, foi de 19,5% para o genótipo TT; 44,2% para TG e 32,1% para GG. Encontrou-se, nas amostras de pacientes, uma frequência de 14,9% para o genótipo TT, 77,2% para TG e 31,8% para GG. Nos controles observou-se uma frequência de 24,1% para o genótipo TT, 41,5% para TG e 30,4% para GG. **Conclusões:** O presente estudo demonstrou maior incidência do polimorfismo +114G/T na amostra controle, sugerindo um efeito protetor para o CM na amostra de mulheres de Mato Grosso.

DESCRITORES: Câncer de mama; Polimorfismo genético; Interleucinas.

INTRODUCTION

Breast cancer (BC) is a malignant tumor of great incidence among women, accounting for approximately 3% of deaths due to neoplasia in this genre[1,2].

BC occurs when mammary cells, especially those located in the mammary ducts, go through mutations and begin to divide and reproduce in a fast and disorderly way. It affects mainly women around the age of 50, being less frequent among those aged below 35 years old[3]. In general, the first sign of the disease is characterized by the presence of a nodule of varying size and location; other less frequent symptoms are breast retraction, breast deformity, presence of enlarged axillary nodes, pain and edema[4].

The etiology of BC may be classified as sporadic or hereditary. About 90% of the cases are sporadic with a multifactorial model, i.e., they result from a strong interaction between genetic and environmental components. The remaining ones represent hereditary cases[3]. Mutations in the BRCA1 and BRCA2 tumor suppressor genes confer an increased risk of developing BC[5].

Given the complex nature of the sporadic cases, it is necessary to investigate other mechanisms which may influence their appearance. Studying the genes involved with the human immune system is a perspective to be considered.

Cytokines are multiple action glycoproteins secreted by different cells of the defense system. The main cytokines sources are T lymphocytes, especially the auxiliary ones. Some cytokines are named interleukins, which are proteins involved in the process of communication between lymphocytes[7].

Interleukin-2 (IL-2) is the cytokine involved in the regulation and proliferation of T cells functional activity. The gene responsible for this protein is mapped in 4q26. IL-2 functions include the ability to stimulate the survival and differentiation of T cells, acting out as a growth factor for immunological cells and increasing cellular cytolytic activity, promoting the production of immunoglobulin by B lymphocytes. Furthermore, IL-2 contributes to the regulation of clonal expansion and the apoptosis process performed between T and infected cells[8,9].

Recent studies emphasized the role of IL-2 as a promising agent for the activation of the immune response against tumors, playing an essential part in antitumor immunity and displaying inhibition effects to the growth and dissemination of tumor metastases[10,11].

Several polymorphisms in IL-2 have been identified, among which the single nucleotide polymorphism (SNP) +114G/T. This polymorphism is located in the first exon of the IL-2 gene, whose alteration in the base, although silent, abolishes a cleavage site for endonuclease restriction. Studies demonstrate this polymorphism influences the production of IL-2, as well as the disease susceptibility[12].

The present study had the objective of investigating +114G/T polymorphism among women from Mato Grosso and their possible association with BC.

METHODS

It is an epidemiological case-control study. The population of the study consisted of 497 adult female subjects, of which 254 cases and 243 controls, living in Mato Grosso. The sample was obtained by the recruitment of patients in reference oncology services in the municipality of Cuiabá, Mato Grosso, Brazil.

The cases consisted of patients diagnosed through positive histopathologic tests for BC, while the control group consisted of women who had a negative mammography examination for this neoplasm. The present study was approved by the Ethics Committee of the *Universidade de Cuiabá* (No. 308. CEP UNIC 0307-308).

The genomic deoxyribonucleic acid (DNA) was obtained from the lymphocytes present in peripheral blood and the DNA extraction technique used followed the protocol described by Lahiri and Nurnberger, with changes[13]. The Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) technique was used in order to identify the +114G/T polymorphism (rs2069763) in the IL-2 gene. The primers used were 5' ATGTACAGGATGCAACTCCT-3' (forward) and 5' TGGTGAGTTTGGGATTCTTG-3'(reverse)[11,14]. The conditions of the Polymerase Chain Reaction (PCR) consisted of an initial denaturation of 94ºC for 5 minutes, annealing temperature of 63ºC for 2 minutes and 72ºC for 1 minute; followed by 30 cycles of 94ºC for 30 seconds, 63ºC for 45 seconds and 72ºC for 45 seconds. The final extension was carried out under a temperature of 72ºC for 8 minutes and 4ºC for 15 minutes. PCR products were digested at 37ºC for 12 hours with restriction MWOI enzyme (New England). The digestion products were visualized through electrophoresis in 8% polyacrylamide. The fragments obtained were sized 262pb, 151pb and 111pb corresponding to the TT, TG and GG genotypes, respectively. The quantitative independent variables were analyzed and evaluated by the χ^2 test, with confidence interval of 95% (95% CI). The value of $p<0.05$ was considered statistically significant.

RESULTS

The characterization of the studied population showed that the mean age of patients was 50.79 ($\pm$10.76) years old and controls were aged 47.2 ($\pm$9.55) years, showing a balance between groups regarding age. There was no predominance of ethnicity among patients, though there was a predominance of non-white/Caucasian subjects in the control group. As for the variable of menarche age, 43.3% of patients had their first menstrual period before 12 years of age and 49.6% had it after 12 years of age. In the control group, it was observed that 57.2% of subjects had their first menstrual period after 12 years of age and 40.3% had it before that. About 51.6% of patients had already gone through menopause. The control group was more homogeneous for this variable. About 61% of patients did not have family history of BC.

Alcohol intake and smoking habits were more frequent in the control group: 81.9 and 59.7%, respectively. The results regarding the number of pregnancies were balanced among the analyzed groups. Both presented higher frequency for three or more pregnancies. When analyzing the age of the first pregnancy, 58% of control women reported having had their first pregnancy before 20 years of age, followed by 32.5% who had their first pregnancy between 21 and 30 years of age and only 2.5% after 30 years of age. In the patients sample, 37.4% of them had their first pregnancy between 21 and 30 years of age, followed by 36.6% before the age of 20 and 9.1% after 30 years of age. The variable regarding the use of contraceptive presented relevant results, in which 89.3% of the control sample used this medication and 8.6% of it did not do so. The patient group had greater homogeneity for contraceptive use: 53.5% reported its use and 38.6% did not use it. Another difference was found when analyzing the results for hormonal therapy. In the patients group, only 13.4% of the sample reported the use of hormonal therapy at some point in their lives, while 89.3% of the control group sample referred to this use. Only 8.6% of the interviewees in the control group did not use hormonal therapy, while 78.3 of patients did not use it at any point in their lives. There was no difference between groups regarding the breastfeeding (for at least three months) variable. As for the clinical and laboratory aspects of the patients, it was observed that 47.1% of the sample presented positive estrogen receptor and 34.5% a negative one. When observing the progesterone receptor variable, a greater frequency of positive women was observed. Most patients had tumors between 2 and 5 cm. The patients group had a slight variation when comparing the presence or absence of affected lymph nodes: 47.5% of them did not present affected lymph nodes, while 32.5% of them reported their presence. When analyzing the frequency of symptoms, it was noted that about 49.4% of them developed a nodule as the first symptom. Many patients (44.7%) reported having found out about their disease through self-examination, and the remainder through mammography, medical consultations and ultrasonography. As for the immunohistochemical analysis regarding p53, her2 and ki67, it was observed that 45.1% of the sample was negative for p53 and the remaining ones were positive. About 50.2% of the sample was negative for the presence of her2. Most of the sample — about 66.7% — displayed the presence of ki67. When inquired about self-examination 51.8% of the subjects stated they perform it, while 20.4% of them reported not having this habit. (Table 1)

The analysis of the frequency distribution of +114G/T polymorphism showed that, both in the patients and the control group, the most evident genotype for polymorphism was TG, followed by GG and TT frequencies. The control group presented higher numbers of polymorphic TT genotype, when compared to the patients group. About 60.8% of the TT genotype was found in the control group, while only 39.1% was found

Table 1. Epidemiological characterization of cases and controls of breast cancer in women from Mato Grosso, Brazil

Characteristics	Cases	Controls
Age		
Mean	50.79	47.2
SD	10.76	9.55
Ethnicity		
White/Caucasian	120 (47.2%)	64 (26.3%)
Non-White	116 (45.6%)	173 (71.2%)
Did not answer	21 (7.2%)	6 (2.5%)
Menarche age		
Up to 12	110 (43.3%)	98 (40.3%)
More than 12	125 (49.6%)	139 (57.2)
Did not answer	19 (7.4%)	6 (2.5%)
Menopaused		
Yes	131 (51.6%)	116 (47.7%)
No	104 (40.9%)	121 (49.8%)
Did not answer	19 (7.5%)	6 (2.5%)
Family history of breast cancer		
Yes	80 (31.5%)	
No	155 (61.0%)	
Did not answer	19 (7.5%)	243 (100%)
Alcoholism		
Yes	45 (17.7%)	199 (81.9%)
No	189 (74.4%)	36 (14.8%)
Did not answer	20 (7.9%)	8 (3.3%)
Smoking		
Yes	61 (24%)	145 (59.7%)
No	174 (68.5%)	55 (22.6%)
Did not answer	19 (7.5%)	43 (17.7%)
No. of pregnancies		
Did not have children	29 (11.4%)	13 (5.3%)
Up to 2	81 (31.9%)	88 (36.2%)
3 or more	126 (49.6%)	137 (56.4%)
Did not answer	18 (7.1%)	5 (2.1%)
Age of the 1st pregnancy		
Up to 20	93 (36.6%)	141 (58.0%)
Between 21 and 30	95 (37.45%)	79 (32.5%)
More than 30	23 (9.1%)	6 (2.5%)
Did not answer	43 (17.0%)	17 (7.0%)
Use of contraceptive		
Yes	136 (53.5%)	217 (89.3%)
No	98 (38.6%)	21 (8.6%)
Did not answer	20 (7.9%)	5 (2.1%)
Use of Hormonal Replacement Therapy		
Yes	34 (13.4%)	217 (89.3%)
No	199 (78.3%)	21 (8.6%)
Did not answer	21 (8.3%)	5 (2.1%)
Breastfeeding (>3 months)		
Yes	165 (64.9%)	204 (83.9%)
No	64 (25.1)	25 (10.2%)
Did not answer	25 (9.8%)	14 (5.7%)
Total	254 (100.0%)	243 (100.0%)

in the patients group. The remaining genotypes, TG and GG, were observed in a more evenly balanced way when comparing the groups (Table 2).

DISCUSSION

According to the Ministry of Health, age remained the main risk factor for BC in 2012. The present study obtained a mean age for women with BC of about 50 years old, corroborating several previous findings[15]. The White/Caucasian ethnicity was more present in the control group, according to a study published by the National Institutes of Health Consensus Development, in 2001, based on the population of the United States of America. It was concluded that White patients had greater risk of developing BC when compared to Black ones, also considering that the case group displayed predominance of the White/Caucasian ethnicity. It should be noted that, in the present study, ethnicity was self-reported, a fact which could be considered a limitation, although several other studies follow this same line.

McPherson et al.[15], when studying English women, observed that the number of pregnancies is a relevant component to increase the risk of BC development. However, the present study observed that both the control and the case group had greater incidence of pregnancies number, an evidence that, for the female population of Mato Grosso, the low number of pregnancies did not influence the development of BC. On the other hand, it was observed that the control group showed greater incidence in pregnancies in early ages, while the case group had greater frequencies observed in late pregnancies. This epidemiological data was obtained from a previous study by Vieira et al. (2012)[3], based on the Brazilian population.

When analyzing the use of alcohol and use of cigarette variables, it was observed that most patients did not consume these drugs, while the control group presented greater incidence of their use. The analysis of this variable agrees with a Brazilian study by Rodrigues et al.[2], in which alcohol consumption and smoking habits were considered risk factor for the development of BC. Most of the sample analyzed was obtained in public institutions, which may have caused this contrary result.

The use of hormonal and contraceptive therapy is also considered a risk factor for BC. In this work, the use of contraceptive is not in agreement with the literature, considering that most patients reported not to use it. Therefore, the use of hormonal therapy did not behave as a risk factor for the population of Mato Grosso.

According to McPherson et al.[15], the risk of developing BC is increased among women with a family history of the disease. However, most patients in the present study did not report having any kind of BC family history.

The analysis of the age or menarche variable found a greater frequency, both for case and control groups, for the menarche after 12 years of age, i.e., late menarche — contrary to the findings of previous studies, in Brazil by Rodrigues et al.[2] and Silva et al. (2012)[1] and, in the United Kingdom, by McPherson et al. (1994)[15].

The presence of nodules is considered the main and first symptom of BC; Brazilian studies carried out by Trufelli (2008)[6] and Silva et al. (2012)[1] corroborate this information. This research is in agreement with the literature, showing the presence of nodules as the first sign of neoplasia, like the American study carried out by Mavaddat et al. (2010)[5].

This study had the objective of determining the distribution of +114G/T polymorphism in the IL-2 gene of a female population in Mato Grosso. In a sample of 497 women, between case and control groups, a genotype frequency of 19.5% for TT, 44.2% for TG and 32.1% for GG was observed. In a study carried out in China, Hu et al. (2013)[14] found genotype frequency, for the same polymorphism of this study, of 29.0% for TT, 50.1% for TG, and 20.7% for GG.

Several studies have been carried out with the objective of associating +114 G/T polymorphism in the IL-2 gene with carcinomas and autoimmune pathologies, some with positive association results and others with negative results. Therefore, the objective here was to also demonstrate the association of +114 G/T polymorphism in the IL-2 gene with BC.

According to Lin et al.[11], in a study carried out in Taiwan, in 2008, an association between the presence of +114G/T polymorphism in the IL-2 gene and autoimmune diseases such as sclerosis, arthritis and lupus was observed.

In 2010, a case-control study carried out in China, by Wei et al.[16], associated +114G/T polymorphism in the IL-2 gene with nasopharyngeal carcinoma, although no significant difference was found between the groups. On the other hand, in a case-control study carried out in Taiwan, in 2006, Wu et al.[10] observed a greater prevalence of polymorphism among patients with prostate cancer. Another study carried out in China, in 2012, by Hu et al.[14], showed no association between polymorphism and BC.

The present study observed no statistically significant association between polymorphism and BC, however, a statistical difference was observed (p=0.005) for the control group. The polymorphism in the IL-2 gene may have behaved as a protection

Table 2. Distribution of the frequency of +114G/T polymorphism of the IL-2 gene in women from Mato Grosso, Brazil

Genotype	Patients	Controls	Total	p-value
TT	38	59	97	0.005
TG	119	101	220	
GG	81	79	160	
Not found	16	4	20	
Total	254	243	497	

factor for BC. Previous studies demonstrated that this polymorphism in the IL-2 gene abolishes a restriction site of the MWOI. It is a silent point mutation. However, researches demonstrate that this polymorphism influence the production of IL-2 and the functions of these cytokines include the ability to stimulate the survival and differentiation of T cells, acting as a growth factor for immunological cells and for the promotion of increase cell cytolytic activity. Also it promotes the production of immunoglobulin by lymphocytes B. IL-2, which contributes to the regulation of clonal expansion and the process of apoptosis performed by the cells and, thus, performs and essential function in anti-tumor immunity[10,11].

In the present study, the polymorphism was more frequent in the group of control women for BC. This group consisted of, for the most part, women with habits considered as risky for BC in the literature, such as smoking, alcoholism and use of hormonal therapy. The presence of polymorphism in this group exposed to BC risk factors is suggested to work as a strong protector for this neoplasia.

CONCLUSION

The presence of +114G/T polymorphism in the IL-2 gene behaved as a protection factor for BC in women from Mato Grosso.

REFERENCES

1. Silva PA, Riul SS. Câncer de mama : fatores de risco e detecção precoce. Rev Bras Enferm. 2012;64(6):1016-21.

2. Rodrigues V. Epidemiologia do cancro da mama. Permanyer Portugal. 2010;34(Parte 1).

3. Vieira SC, Lustosa AML, Barbosa CNB, Teixeira, JMR, Brito LXE, Soares LFM, et al. Oncologia Básica. Teresina: Fundação Quixote; 2012.

4. Schwanke CHA, Schneider RH. Atualizações em Geriatria e Gerontologia: da pesquisa básica à prática clínica. Porto Alegre: EdiPUCRS; 2008. 175p.

5. Mavaddat N, Antoniou AC, Easton DF, Garcia-Closas M. Genetic susceptibility to breast cancer. Molecular Oncology [internet]. 2010 [cited on 2016 Apr. 05];4(3):174-91. Available from: http://dx.doi.org/10.1016/j.molonc.2010.04.011

6. Trufelli DC, Miranda VDC, Santos MBB dos, Fraile NMP, Pecoroni PG, Gonzaga SDFR, et al. Análise do atraso no diagnóstico e tratamento do câncer de mama em um hospital público. Rev Assoc Méd Bras. 2008;54(1):72-6.

7. Naoum PC. Citocinas e interleucinas. São José do Rio Preto: Academia de Ciência e Tecnologia de São José do Rio Preto; 2009.

8. Abbas AK, Lichtman AH, Pillai S. Imunologia celular e molecular. 7ª ed. Rio de Janeiro: Elsevier; 2012.

9. Fedetz M, Matesanz F, Caliz R, Ferrer MA, Collado MD, Alcina A, et al. Lack of association between – 384 and 114 IL-2 gene polymorphisms and rheumatoid arthritis. J Rheumatol. 2003;30(3):435-7.

10. Wu H, Chang C, Wan L, Wu C, Tsai F, Chen W. IL-2 Gene C/T Polymorphism is associated with prostate cancer. J Clin Laboratory Analysis. 2006;249(2):245-9.

11. Lin Y-J, Wan L, Sheu JJ-C, Huang C-M, Lin C-W, Lan Y-C, et al. G/T polymorphism in the interleukin-2 exon 1 region among Han Chinese systemic lupus erythematosus patients in Taiwan. Clin Immunol (Orlando, Fla.) [internet]. 2008 Oct. [cited 2013 Apr. 26];129(1):36-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18650128

12. Matesanz F, Delgado C, Fresno M, Alcina A. Allelic selection of human IL-2 gene. Eur J Immunol. 2000;30:3516-21.

13. Lahiri DK, Nurnberger JI. A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. Nucleic acids research [internet]. 1991 Oct. 11 [cited on 2016 mês 05];19(19):5444. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=328920&tool=pmcentrez&rendertype=abstract

14. Hu X-B, Ouyang L-Z, Tang L-L. Interleukin-2 gene polymorphisms and prognosis of breast cancer. Genet Test Mol Biomarkers [Internet]. 2013 Jun. [cited 2013 Apr. 26];17(6):453-7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23477313

15. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer--epidemiology, risk factors and genetics. BMJ . 2000;321:624. DOI:10.1136/bmj.321.7261.624.

16. Wei, YS, Lan, Y, Zhang, L, Wang, JC. Association of the interleukin-2 polymorphism with interleukin-2 serum levels and risk of nasopharyngeal carcinoma. DNA and cell biology. 2010;29(7):363-8. DOI: 10.1089/dna.2010.1019.

PHYLLODES TUMORS OF THE BREAST: A RETROSPECTIVE EVALUATION OF CASES FROM THE HOSPITAL DO SERVIDOR PÚBLICO ESTADUAL DE SÃO PAULO

Tumor filoides de mama: avaliação retrospectiva de casos do Hospital do Servidor Público Estadual de São Paulo

Ana Beatriz Tavares de Moura Brasil Matos[1]*, Joaquim Teodoro de Araujo Neto[2], Marcelo Antonini[1], Odair Ferraro[1], Bruno de Carvalho Mancinelli[3], Ana Maria Gomes Pereira[1,3], Reginaldo Guedes Coelho Lopes[1,3]

ABSTRACT

Objective: To evaluate the clinical and pathological characteristics of phyllodes tumors, and to identify possible associated risk factors for relapses among patients from the Breast Surgery Department of the Hospital do Servidor Público Estadual of São Paulo (HSPE-SP). **Methods:** Retrospective, descriptive study of data from 52 patients, between 1976 and 2013. The following data were collected: age, tumor size, histological type, surgical margins, type of surgery performed, relapses and amount of time before relapse. **Results:** The mean age of the patients was 45.7 years old, the mean size of the tumor was 7.8 cm. A mastectomy was performed on 12 patients, and the others underwent a wide excision. Benign phyllodes tumors were found in 30 patients, and the others were found as follows: 11 with borderline tumors and 11 with malign phyllodes tumors. There was no statistical relevance with regard to the relapses and the characteristics evaluated. **Conclusion:** The sample studied has similar clinical and pathological characteristics as described in the scientific literature, with the mean age at diagnosis being 45 years old, the mean tumor size, 7.8 cm. The majority found were benign phyllodes tumors and 33% were from relapses. There was no statistical significance between the evaluated variables and the risk for relapse.

KEYWORDS: Breast disease; Surgery; breast tumors; Phyllodes tumors; breast.

RESUMO

Objetivo: Avaliar as características clínicas e patológicas do tumor filoides e identificar fatores relacionados com risco de recidivas em pacientes acompanhadas no ambulatório de Mastologia do Hospital do Servidor Público Estadual de São Paulo (HSPE-SP). **Método:** Estudo retrospectivo descritivo de dados de 52 pacientes, entre 1976 e 2013, dentre os quais: idade, tamanho do tumor, tipo histológico, margens cirúrgicas, tipo de cirurgia, recidivas e tempo para recidiva. **Resultados:** A idade média das pacientes foi 45,7 anos. O tamanho médio do tumor foi de 7,8 cm. O tratamento em 12 pacientes foi a mastectomia, e as demais 40 a excisão ampla. O tipo histológico encontrado em 30 pacientes foi tumores benignos, 11 malignos e 11 de variedade borderline. Após o seguimento médio de 53,93 meses, observaram-se 17 recidivas. Não houve relevância estatística entre a recorrência local e as variáveis avaliadas. **Conclusões:** A amostra avaliada tem características clínicas e patológicas condizentes com a literatura, com média de idade de 45 anos, tamanho do tumor de 7,8 cm, sendo encontrados na maioria tumor filoides benigno e 33% de recidivas. Não houve significância estatística entre características avaliadas e o risco de recidiva.

PALAVRAS-CHAVE: Doenças da mama; cirurgia; tumores de mama; tumor filoide; mama.

INTRODUCTION

Phyllodes tumor of the breast is a rare type of neoplasm, and accounts for less than 1% of all breast tumors[1-3]. It was described in 1838 by Johannes Mueller, under the name of Cystosarcoma Phyllodes, for having cystic content (cysto), flesh-like aspects (sarcoma) and foliaceous extensions (phyllodes)[4,5].

The etiology of phyllodes tumors remains unknown. They mainly appear women and rarely occur in the male sex. Only nine cases have been described in the literature of men with gynecomastia. Its incidence is apparently higher in white women, in the age group of 35-55 years old[6].

In 1982, the World Health Organization (WHO)[7] grouped more than 60 types of tumors in the classification of phyllodes tumors, because it was the most appropriate classification for grouping all of their characteristics. After the study done by Trevor, Norris and Azzopardi, the WHO adopted the pathological subclassifications of benign, borderline and malignant, which are used today (Chart 1). However, the classifications do not predict the clinical and biological behavior of this neoplasm[1,8-10].

Histologically, phyllodes tumors are diverse with regard to the way they present themselves. Sometimes they resemble fibroadenoma and, at other times, they resemble a low-grade sarcoma, since these tumors are formed by epithelial and stromal elements of the breast. Characteristically, their intracanalicular growth pattern resembles a tree leaf[4,5]. The classification into benign, malignant or borderline is done by analyzing the tumors' stromal components: stromal cell atypia, mitosis index, stromal cellularity and aspects of the margins[1-3,5].

Benign phyllodes tumors are characterized by the absence of or the mild presence of stromal cellular atypia, discrete or circumscribed stromal hypercellularity, circumscribed margins, and mitotic activity of less than 5 mitoses per 10 high-power fields (10 HPF). Borderline tumors have mild or moderate stromal atypia, moderate hypercellularity, circumscribed or infiltrative margins, and mitotic activity between 5-10 mitoses per 10 HPF. Malignant phyllodes tumors are characterized by pronounced stromal atypia, enhanced, usually marked and diffuse hypercellularity, infiltrative margins, and a mitosis index greater than 10 mitoses per 10 HPF[5,11].

A phyllodes tumor macroscopically is a circumscribed, rounded or oval-shaped nodule, which may be multinodular and devoid of a true capsule. The literature reports tumor sizes from 1 cm to larger than 40 cm. Upon macroscopic examination, phyllodes tumors are quite similar to fibroadenoma[4,5].

Clinically, it is a single, unilateral, solid, rapidly growing, large-sized tumor that can cause bulging, distortion or ulceration of the skin[1,2,12]. There are no determinant risk factors for the onset of phyllodes tumors, but patients with a p53 mutation and Li-Fraumeni syndrome are at a high risk for developing these lesions[5].

The diagnosis of phyllodes tumors should be made using both medical history and physical examination. Complementary imaging studies may show lesions that are often confused with fibroadenoma. Even the anatomopathological analysis of the material obtained by biopsy, either by fine needle aspiration (FNA) or by fragment biopsy, raises doubts about the etiology of the tumor[3,5].

If, clinically, there is suspicion that the tumor is present, surgical treatment for the complete removal of the lesion with adequate margins is the standard procedure, and a broad excision with margins, or even a simple mastectomy may be indicated to avoid recurrences[1,3,13,14].

The prognostic factors associated with relapses are still not well established. Ward et al. describes stromal hypercellularity as a factor that would influence the prognosis[5]. Later, in 1991, Cohn-Cedermark et al. included tumor necrosis and the presence of different fibromixoid tissue factors among the prognostic factors[16].

A study by Mokbel et al.[17], demonstrated that there is an association between the local recurrence of phyllodes tumors and the histological type, with a higher recurrence rate among patients with malignant phyllodes tumors.

Other case series studies, such as the one carried out by Roos et al.[18], observed that local recurrence was more significant when the surgical margins were affected by the tumor.

This study aims to evaluate the clinical and pathological characteristics of the phyllodes tumor in patients treated at the mastology outpatient clinic of the Hospital do Servidor Público Estadual de São Paulo. It compares them with those in the literature, and also evaluates if there is any risk factor associated with the recurrence of phyllodes tumors after surgical treatment.

METHODOLOGY

A retrospective analysis of medical records was carried out with patients from the Hospital do Servidor Público Estadual de São Paulo, from 1993 to 2013, who had a clinical and histopathological diagnosis of phyllodes tumors and who underwent treatment at the mastology outpatient clinic. Only medical records of patients that were confirmed to have a histopathological tumor type were included in the study, totaling 29 cases. Cases that were not confirmed to be histopathological, like benign tumors such as fibroadenoma, and malignant tumors such as breast cancer and sarcomas, were not included (Table 1).

This study included data from the series of 23 cases of the retrospective study on phyllodes tumors carried out in the same hospital from 1976 to 1992, by Araújo Neto et al., and published in Mastology — the Official Journal of the Brazilian Society of Mastology — in 1999[4]. There was a total of 52 cases.

The clinical and histopathological aspects of each patient that were contained in the medical records were reviewed. Data such as age at diagnosis, affected breast, type of surgery performed,

tumor size, follow-up time, and relapses, were collected. With regard to the histopathological diagnosis, the margins were evaluated and were considered to be free when they were greater than or equal to 1 mm. The tumors were classified according to the WHO's categories[7] into benign, borderline and malignant. The data were distributed in a standardized table using Microsoft Office Excel 2013 for interpretation.

The study by Araújo Neto et al.[4] did not analyze surgical margins or the histological type of the tumor and relapse. Thus, a statistical analysis was performed with only 30 patients, in which it was possible to describe the data about the surgical margins and the histological type of tumor, in which there were recurrences. Other data were evaluated together.

A descriptive and retrospective data analysis was performed. For the statistical analysis of the results, the SPSS 22.0 software was used, considering p (level of descriptive significance) less than 0.05 as significant.

RESULTS

The mean age of the patients at the time of diagnosis was 45.7 years old (and ranged from 17-82 years old). The mean tumor size was 7.8 cm (and ranged from 3 to 17 cm). Of the total number of patients, 12 underwent a mastectomy. The remaining 40 underwent an extensive excision procedure. Of the 52 tumors examined, 30 were benign, 11 were malignant, and 11 were borderline. After the mean follow-up of 53.93 months, 17 recurrences were observed (Table 2).

Among the 30 patients whose data on surgical margins and histological type of relapse could be determined, there were nine recurrences, all of which were initially submitted to extensive excision. Three had margins that were compromised by the tumor after the surgery. Among the nine relapses, five of the initial tumor types were benign, three were malignant and one was borderline, as shown in Tables 3 and 4.

The association between local recurrence and histological type was not statistically relevant (Table 5). There was also no relevant statistical association between tumor size and local recurrence.

No significant statistical difference was observed with regard to the age of diagnosis among patients with local recurrence and patients without it.

DISCUSSION

Phyllodes tumor of the breast is a rare disease, occurring mostly in women aged between 35-55 years old[6]. The study by Lenhard et al.[6] with a sample of 33 cases, had an average age of 47 years old. The study by Hassouna et al.[19], with a sample of 106 patients, had a mean age of 39.6 years old, and Karim et al.[20] reported a mean age of 43 years old. The present study demonstrates a similar finding regarding the diagnostic age range, with a mean of 45.7 years old. This reinforces data described in the literature about the age group with the highest rate of onset.

In the studied sample, the mean tumor size found after the histopathological analysis was performed was 7.8 cm, with a wide range of sizes from 3 to 17 cm. The series of case studies in the literature show varying results, such as 0.5 to 25 cm in the study by Hassouna et al.[19], and 0.4 to 29 cm in the study by

Table 2. Characteristics of patients and treatment modalities.

Age (years)	
Mean	45.7
Interval	17-82
Size (cm)	
Mean	7.8
Interval	3-17
Type of surgery	
Broad excision	40 (77.0%)
Mastectomy	12 (23.0%)
Histological type of tumor	
Benign	30 (57.8%)
Borderline	11 (21.1%)
Malignant	11 (21.1%)
Surgical margins	
Free	22 (73.3%)
Affected	8 (26.7%)
Recurrences	17 (33.0%)
Total patients	52

Values in parentheses are the percentages. The margins that were considered free were those in which "cells do not touch the ink". In this study, only information about the margins of 30 patients was obtained.

Table 1. Histological classification of phyllodes tumors.

Characteristic	Benign	Borderline	Malignant
Mitotic activity	<5/10 HPF	5-9/10 HPF	>=10/10 HPF
Stromal atypia	Absent or mild	Mild or moderate	Enhanced
Stromal cellularity	Discrete, non-uniform or diffuse hypercellularity	Moderate, non-uniform or diffuse hypercellularity	Enhanced, usually marked and diffuse hypercellularity
Margins	Circumscribed	Circumscribed or infiltrative	Infiltrative

Source: World Health Organization[7].

Table 3. Characteristics of patients with a recurrence of phyllodes tumors.

Age (years)	
Mean	45.7
Interval	17-64
Size (cm)	
Mean	8.1
Interval	4-15
Type of surgery	
Broad excision	14 (82.3%)
Mastectomy	3 (17.7%)
Histological type of tumor	
Benign	9 (53.0%)
Borderline	5 (29.4%)
Malignant	3 (17.6%)
Disease-free interval (months)	
Mean	37.8
Interval	5–120
Total patients	17

There was no result with p<0.05.

Table 4. Surgical margins in 9 recurrences of phyllodes tumors.

Surgical margins	
Free	6 (66.6%)
Affected	3 (33.3%)
Total patients	9

p=0.244; CI=0.473 to 19.039.

Table 5. Histological type of the recurrence of 30 patients with phyllodes tumor recurrence.

Histological type of recurrence	
Benign	4 (44.4%)
Borderline	3 (33.3%)
Malignant	2 (22.2%)
Total patients	9

In this study, information about histological type of recurrence was obtained only in 9 patients.

Spitaleri et al.[1]. No study was able to statistically establish any significant relationship between tumor size and local recurrence. Despite the fact that there was no statistical significance, it is possible to observe in the literature that local control is hampered by larger tumors. Patients with tumors larger than 5 cm have a lower chance of survival according to a study by Belkacemi et al.[21].

Phyllodes tumors are usually treated with wide excision surgery with adequate margin resection. Simple enucleation should be avoided. Obtaining an adequate margin of normal breast tissue – about 1 or 2 cm for some studies and negative margin for others – is especially important in the case of borderline or malignant tumors, since surgical margins are the best predictor of local recurrence[6,16].

Mastectomy is no longer considered the treatment of choice for phyllodes tumors, even borderline or malignant ones, in cases in which wide excision with margins is feasible, since local recurrence is not associated with systemic metastases and can be treated with a new wide excision[1,4,6,16,21].

In this study, malignant and borderline tumors accounted for an incidence rate of 21.1% each, indicating a total of 42.2%. This incidence was similar to that found in the literature review, carried out by Spitaleri et al. (2013)[1], who analyzed 5,530 patients and found malignant and borderline phyllodes tumors in about 48%, almost half of the sample. Another series of case studies by Mokbel et al. (1999)[17] with 30 patients, and Belkacemi et al. (2008)[21] with 443 patients, showed a slightly lower incidence, with 30 and 36%, respectively, between borderline and malignant tumors.

Due to the rarity of this neoplasm and the difficulties in anatomopathological classification, many discordant results are found in the literature. Authors, in order to obtain a relevant number of patients for the statistical analysis, seek cases in extensive databases with samples from many years, which in turn damages the homogeneity of the studied group. An example of this is the diversity of the prevalence of histological types, since this anatomopathological analysis is observer-dependent. Despite the established criteria for diagnosis, differences in each medical professional's analysis and individual perception always exist. In addition, since 1982, there have been several histological reclassifications of phyllodes tumors, which impairs the uniformity of the data.

In this study, the percentage of large excision procedures with adequate margins among the 30 patients that could be evaluated was 86.7%. Of these, 26.7% had margins that were compromised by the disease, which was 8 patients. In the group of patients with compromised margins, half had recurrence. In spite of the impairment of the prevailing margin in the studies as a factor that leads to recurrence[5,17,19,21,22], the present study did not succeed in statistically corroborating this relationship, probably due to the small number of patients in the sample.

CONCLUSION

The sample of patients analyzed at the Hospital do Servidor Público Estadual de São Paulo has similar clinical and pathological characteristics to those in the literature, with a mean age of 45 years, and a tumor size of 7.8 cm. Mostly benign phyllodes tumors were found and 33% had relapses.

It was not possible to infer if any of the characteristics evaluated influenced the recurrence of phyllodes tumors. This is justified by the low incidence of this tumor, resulting in a small sample. The literature review on the subject also cannot demonstrate studies that definitively associate one factor as the prognosis or the predictor of recurrence, which reinforces the difficulty in understanding and defining the biological behavior of this rare neoplasm. Further work and studies need to be conducted to determine prognostic and predictive factors for the recurrence of phyllodes tumors.

REFERENCES

1. Spitaleri G, Toesca A, Botteri E, Bottiglieri L, Rotmensz N, Boselli S, et al. Breast phyllodes tumor: A review of literature and a single center retrospective series analysis. Crit Rev Oncol Hematol. 2013;88:427-36.

2. Lima LNB, Pedrosa MC, Novita G, Luzzatto F, Frasson A. Tumores não epiteliais. In: Frasson A, Millen E, Novita G, Zerwes F, Brenelli F, Luzzatto F, et al. Doenças da Mama. São Paulo: Atheneu; 2013. p.359-64.

3. Foxcroft LM, Evans EB, Porter AJ. Difficulties in the pre-operative diagnosis of phyllodes tumours of the breast: A study of 84 cases. The Breast. 2007;16:27-37.

4. Araújo Neto JT, Depes D, Alcântara M, Ferraro O, Baracat F. Tumor Filóides (Cistossarcoma Filóides). Rev Bras Mastologia. 1999 Mar;9(1):28-33.

5. Calhoum KE, Lawton TJ, Kim JN, Lehman CD, Anderson BO. Phyllodes tumors. In: Harris JR, Lippman ME, Morrow M, Osborne CK. Diseases of the Breast. 4ª ed. Philadelphia: Lippincott Williams & Wilkins; 2010. p.781-92.

6. Lenhard MS, Kahlert S, Himsl I, Ditsch Nina, Untch M, Bauerfeind I. Phyllodes tumour of the breast: Clinical follow-up of 33 cases of this rare disease. Eur J Obstet Gynecol Reprod Biol. 2008;138:217-21.

7. World Health Organization. The World Health Organization: Histological typing of breast tumors - second edition. Am J Clin Pathol. 1982;78:806-916.

8. Azzopardi JG. Sarcoma in the breast. In: Azzopardi JG, editor. Problems in breast pathology. Philadelphia: WB Saunders; 1979. p.346-65.

9. Treves N, Sunderland DA. Cystosarcoma phyllodes of the breast: amalignant and a benign tumor; a clinicopathological study of seventy-seven cases. Cancer. 1951;4(6):1286-332.

10. Norris HJ, Taylor HB. Relationship of histologic features to behavior of cystosarcoma phyllodes analysis of ninety-four cases. Cancer. 1967;20(12):2090-9.

11. Tan HP, Ellis IO. Myoephitelial and epitelial-myoepithelial, mesenchymal and fibroepithelial breast lesions: updates from the WHO Classifications of Tumours of the Breast 2012. J Clin Pathol. 2013;66:465-70.

12. Velásquez-Dohom M, Gamboa-Domínguez A, Medina-Franco H. Phyllodes tumor of the breast: clinicopathologic analysis of 22 cases. Rev Invest Clin. 2013 May-Jun;65(3):214-20.

13. Sawalhi S, Al-Shatti M. Phyllodes tumor of the breast: a restrospective study of the impact of histopathological factors in local recurrence and distant metastasis. Ann Saudi Med. 2013 Mar-Apr;33(2):162-8.

14. Majeski J, Stroud J. Malignant phyllodes tumors of the breast: a study in clinical practice. Int Surg. 2012 Apr-Jun;97(2):95-8.

15. Ward RM, Evans HL. Cystosarcoma phyllodes: a clinicopathologicstudy of 26 cases. Cancer. 1986;58(10):2282-9.

16. Cohn-Cedermark G, Rutqvist LE, Rosendahl I, Silfverswärd C. Prognostic factors in cystosarcoma phyllodes. A clinicopathologic study of 77 patients. Cancer. 1991;68(9):2017-22.

17. Mokbel K, Price RK, Mostafa A, Wells CA, Carpenter R. Phyllodes tumour of the breast: a retrospective analysis of 30 cases. Breast. 1999;8:278-81.

18. Roos WK, Kaye P, Dent DM. Factors leading to local recurrence or death after surgical resection of phyllodes tumours of the breast. Br J Surg. 1999;86:396-9.

19. Hassouna JB, Damak T, Gamoudi A, Chargui R, Khomsi F, Mahjoub S, et al. Phyllodes tumour of the breast: a case series of 106 patients. Am J Surg. 2006;192:141-7.

20. Karim RZ, Gerega SK, Yang YH, Spillane A, Carmalt H, Scolyer RA, et al. Phyllodes tumours of the breast: a clinicopathological analysis of 65 cases from a single institution. Breast. 2009;18:165-70.

21. Belkacemi Y, Bousquet G, Marsiglia H, Ray-Coquard I, Magné N, Malard Y, et al. Phyllodes tumour of the breast. Int J Radiat Oncol Bio. 2008;70(2):492-500.

22. Khosravi-Shari P. Management of non metastatic phyllodes tumour of the breast: Review of the literature. Surg Oncol. 2011;20:e143-8.

OBESITY AND BREAST CANCER: ADIPOKINES' ROLE

Obesidade e câncer de mama: o papel das adipocinas

Eni Devay de Freitas[1]*, Marco Antonio Vasconcelos Rego[1]

ABSTRACT

Objective: Obesity and overweight are risk factors, and also prognostic factor for cancer, including breast cancer. Studies have accessed adipokines, adiponectins and leptins as keymediators in obesity and breast cancer. **Methods**: This is a systematic review of observational epidemiological cohort, case-control and survival studies related adiponectin and leptin with obesity and breast cancer over the past 15 years. Fourteen studies met the inclusion criteria, assessing the relationship of adiponectin and leptin as a risk factors and prognostic in breast cancer. **Results**: The studies showed an inverse relationship of adiponectin and direct relationship of leptin with body mass index (BMI) and were consistent in assigning lower serum levels of adiponectin to an increased risk of breast cancer, independently of BMI and variables of insulin resistance. Patients with breast cancer have low serum levels of adiponectin and higher levels of leptin in comparison to healthy patients. Low concentration of adiponectin increases the risk of breast cancer, and low concentrations of adiponectin and high of leptin are worse prognosis no matter the factors for breast cancer in women. **Conclusion**: The adipokines, in complex and interrelated mechanisms, probably drive breast cancer initiation and progression.

KEYWORDS: Breast cancer; obesity; adiponectin; leptin.

RESUMO

Introdução: A obesidade e o sobrepeso são fatores de risco e prognóstico para o câncer em diferentes sítios, incluindo a mama. Estudos têm avaliado o papel das adipocinas, adiponectina e leptina, como mediadores-chave entre a obesidade e o câncer de mama. **Métodos**: Foi realizada uma revisão sistemática da literatura de estudos epidemiológicos observacionais do tipo coorte, caso-controle e de sobrevida que relacionavam a adiponectina e/ou a leptina com obesidade e câncer de mama nos 15 anos anteriores à pesquisa. Quatorze estudos preencheram os critérios de inclusão, avaliando a adiponectina e a leptina como fatores de risco e prognóstico para o câncer de mama. **Resultados**: Os estudos demonstraram uma relação inversa da adiponectina e uma relação direta da leptina com o índice de massa corporal (IMC), e foram concordantes em atribuir menores níveis séricos de adiponectina a um aumento no risco de câncer de mama, independentes do IMC e das variáveis de resistência à insulina. As pacientes com câncer de mama apresentaram níveis séricos baixos de adiponectina e altos de leptina, em relação às pacientes saudáveis; níveis séricos baixos de adiponectina e altos de leptina são fatores de pior prognóstico independentes para câncer de mama em mulheres. **Conclusão**: As adipocinas, em mecanismos complexos e inter-relacionados, provavelmente dirigem o aparecimento e a progressão do câncer de mama.

PALAVRAS-CHAVE: Câncer de mama; obesidade; adiponectina; leptina.

INTRODUCTION

Obesity is a current public health problem directly related to the modern "obesogenic" environment, which stimulates the "fast" and exaggerated consumption of high-calorie food and a sedentary lifestyle[1]. Overweight and obesity are risk factors for cancer in different primary sites, including the breast[2]. Obese women are 50% more likely to develop breast cancer than non-obese ones[2]. When diagnosed with breast cancer, obese women tend to present tumors with biological characteristics of greater aggressiveness[3], as well as higher rates of relapse and progression of the disease in their evolution and reduction in survival, in relation to non-obese women[4].

Epidemiological evidence correlates obesity as a worse prognosis risk factor for breast cancer, although the mechanisms related to carcinogenesis are still being studied and are not fully understood. It is postulated that the increased estrogenic stimulus related to obesity[5] and the adipose tissue dysfunction — determining metabolic disorders such as insulin resistance, chronic inflammation and alteration in the adipokine secretion by adipocytes — are the keymediators of breast cancer and obesity[6,7]. Adiponectin and leptin are adipokines responsible for controlling the energy metabolism of the body, satiety, insulin sensitivity, lipid metabolism and acute inflammatory response[8]. They have been related to the risk of cancer, including endometrial, rectum and breast cancer[9,10]. The imbalanced leptin and adiponectin secretion in obesity is implicated in pro-tumorigenic growth and proliferation activation pathways — such as PI3K, ERK and JAK/STAT3 —, angiogenesis stimulation, invasion and metastasis by tumor cells[11,12].

The adipokine's action potential in breast cancer has been studied, and may offer, in addition to understanding the pathophysiology of the disease, new perspectives for cancer prevention, the detection of biomarkers and possible future therapeutic targets[13].

This article had the objective of reviewing epidemiological studies on obesity and adipokines — adiponectin and leptin — on the risk and prognosis of breast cancer, among pre- and postmenopausal women, in the 15 years prior to the survey.

METHODS

It is a systematic review of the literature, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model[14] of epidemiological studies on the relation between obesity, breast cancer and adipokines. The PubMed database was searched for articles published between 1990 and 2016 using the descriptors *breast cancer*, *obesity* and *adiponectin* or *leptin*. The search resulted in 260 articles for the descriptors *breast cancer*, *obesity* and *leptin*; for the descriptors *breast cancer*, *obesity* and *adiponectin*, there were 142 articles.

Articles, written in English, referring to observational, cohort, case-control and survival epidemiological studies were selected, which assessed adiponectin and/or leptin as risk factors or prognosis for breast cancer with obesity, presenting an association measure as relative risk, *odds ratio* (OR) or hazard risk (HR). Basic research, clinical trials, review articles and meta-analyses were disregarded. At the end of the selection and evaluation, only 18 articles were observational epidemiological studies. Of these, four were descriptive ones and did not present the aforementioned association measures, thus being excluded. Finally, 14 studies met the inclusion criteria for the analysis, which was carried out considering the specific information of each article, related to serum levels of leptin and adiponectin or the expression of leptin or adiponectin receptors in tumor pieces, resulting in the relation between risk and/or breast cancer prognosis (Figure 1).

RESULTS

The studies evaluated included Asian, European and American populations. Serum levels or the expression of receptors in tumor pieces of adiponectin and leptin with risk or prognosis of breast cancer were correlated with covariables such as the body mass index (BMI) and anthropometric measures related to obesity; serum markers for insulin peripheral resistance (serum insulin dosage, HOWA calculation — homeostasis model assessment for insulin resistance —, blood glucose, insulin-like growth factor level and globulin-bound); inflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor alpha (TNFA), interleukin-6(IL-6); and serum estradiol dosages (Table 1). HOWA = HOWA-IR homeostasis model assessment for insulin resistance

In the Asian population, the study by Miyoshi et al. (2003)[15], of retrospective case-control nature, observed that women
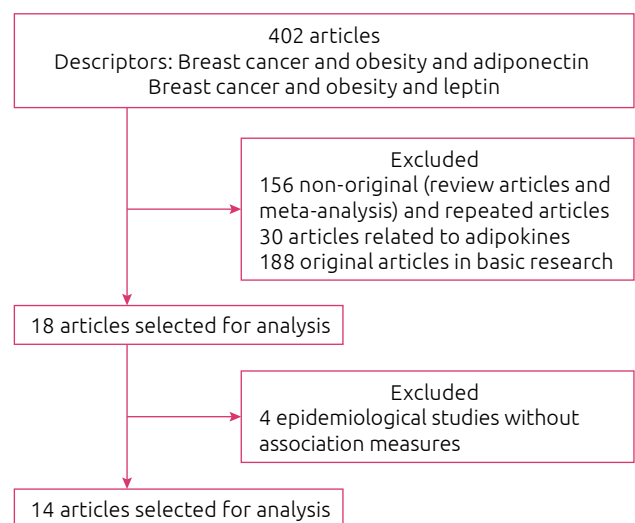

Figure 1. Review article selection flowchart.

with breast cancer had significantly lower levels of serum adiponectin when compared to control patients. The evaluation of serum levels of adiponectin by tertile, adjusted according to age and BMI, evidences that low levels increased the risk for breast cancer: in the lowest tertile, the OR was 3.63 (confidence interval of 95% – 95%CI 1.61–8.19, p<0.005), and in the intermediate tertile, 2.79 (95%CI 1.23–6.35, p<0.050), when compared to the highest serum adiponectin level. Premenopausal women do not have a significant higher risk of breast cancer in intermediate and low adiponectin tertiles, while postmenopausal ones have a significantly higher risk of breast cancer. As for prognosis factors, women with breast cancer and lower adiponectin levels (low tertile) presented a significant higher risk for tumors larger than 2.0 cm (p=0,005) and high grades (p<0.050), which are factors of worse prognosis for this pathology.

The case-control study by Tian et al.[16], with 488 women, related anthropometric measures and serum adiponectin dosage with breast cancer risk. It was observed that central adiposity anthropometrical measures (waist-hip ratio) and the BMI significantly increase the risk of breast cancer only in the postmenopausal period. The BMI was inversely correlated to, statistically significant, serum adiponectin levels, as well as the waist circumference and the waist-hip ratio. Women with elevated serum adiponectin levels had significantly lower risk of developing breast cancer in the postmenopausal period and non-significant risk of it in the premenopausal one, regardless of anthropometric measures. A significant negative association between adiponectin levels and breast cancer was detected in positive estrogen receptor tumor (OR=0.53; 95%CI 0.27–0.98).

The case-control study by Minatoya et al.[17] addressed the association of breast cancer, BMI, insulin levels and serum

Table 1. Distribution of epidemiological studies according to authors, type of study, number of patients, outcomes and covariables.

Author and year	Type of study	N	Adipokine (serum level)	Outcome OR (95%CI) Recurrence, mortality and survival (OS e DDFS)	Covariables
Miyoshi et al., 2003[15]	Case-control	202	Low adiponectin	OR=3.63 (1.61–8.19) Post-M OR=3.90 (1.23–12.44) Pre-M OR=3.48 (0.89–13.50)	BMI
Tian et al., 2007[16]	Case-control	488	High adiponectin	OR=0.55 (0.23–0.97) Post-M OR=0.55 (0.23–0.97) Pre-M OR=0.84 (0.46–1.52)	BMI, anthropometric measures and HR
Minatoya et al., 2014[17]	Case-control	66	High adiponectin	Post-M OR=0.13 (0.03–0.57) Pre-M OR=0.01 (0.00–0.26)	BMI, insulin
Oh et al., 2011[18]	Survival	747	Low adiponectin	Recurrence HR=2.82 (1.03–7.68)	BMI, HOWA-IR, HR
Mantzoros et al., 2004[19]	Case-control	341	High adiponectin	OR=0.84 (0.71–0.99) Post-M OR=0.81 (0.68–0.96) Pre-M OR=0.92 (0.66–1.27)	IGF-1, IGFBP-3
Macis et al., 2012[20]	Survival	214	High adiponectin	Recurrence HR=0.87 (0.79–0.95)	BMI, HOWA-IR, IGF-1, mammographic density HDL
Cust et al., 2008[21]	Case-control	1,122	High leptin	Stages II-IV OR=1.39 (0.65–2.96)	BMI, menopausal status, HR Hb1Ac
Gunter et al., 2015[23]	Case-control	1,714	High adiponectin	OR=0.76 (0.59–1.12) univariate OR=0.81 (0.59–1.12) multivariate	BMI, estradiol
Korner et al., 2007[22]	Case-control	150	High adiponectin	OR=0.35 (0.14–0.88)	BMI, menopausal status
Tworoger et al., 2007[24]	Case-control	3,673	Adiponectin	Post-M OR=0.73 (0.55–0.98) Pre-M OR=1.30 (0.80–2.10)	BMI, IGF-1, IGFBP-3
Harris et al., 2011[25]	Case-control	974	Leptin (interquartile)	OR=0.66 (0.40–0.96)	BMI
Duggan et al., 2010[26]	Survival	1,183	High adiponectin	Mortality reduction 61%	BMI
Gross et al., 2013[27]	Case-control	544	Low adiponectin High leptin	Adiponectin OR=1.63 (1.02–2.60) Leptin OR=2.44 (1.30–4.58)	BMI, TNF
Goodwin et al., 2012[28,29]	Survival	520	High leptin	OS HR=1.92 (1.00–3.69) DDFS HR=1.58 (0.90–2.79) Recurrence HR=1.41 (0.85–2.35)	BMI, insulin

OR: *odds ratio*; 95%CI 95% confidence interval; OS: overall survival; DDFS: distant disease-free survival; Post-M: postmenopausal; Pre-M: premenopausal; BMI: body mass index; HR: hormonal receptors; HOWA-IR: homeostasis model assessment for insulin resistance; IGF-1: insulin-like growth factor 1; IGFBP-3: insulin-like growth factor-binding protein factor 3; HR: hazard risk; HDL: high density lipoprotein; Hb1Ac: glycated hemoglobin; TNF: tumor necrosis factor.

adiponectin. The study showed that serum adiponectin levels were significantly higher in the control group, both in pre- and postmenopausal periods. Adiponectin levels were inversely related to the BMI both in pre- and postmenopausal periods (p=0.001 and 0.002, respectively). There was an association between BMI and breast cancer risk both in premenopausal (OR=1.17; 95%CI 0.23–6.10) and postmenopausal periods (OR=1.39; 95%CI 0.50–3.86). The serum adiponectin level was inversely correlated with breast cancer: high serum adiponectin level reduced the risk of breast cancer in the postmenopausal (OR=0.13; 95%CI 0.03–0.57) and premenopausal periods (OR=0.01; 95%CI 0.00–0.26).

The study by Oh et al.[18] evaluated the recurrence of breast cancer in 747 women, correlating it to levels of serum adiponectin, leptin, insulin resistance markers and metabolic syndrome. The study showed that patients with positive hormone receptor (HR) have significantly higher adiponectin and estradiol levels, and low leptin and homeostasis model assessment for insulin resistance — HOWA-IR levels. In patients with negative HR, the serum adiponectin level had an inverse relation with recurrence (p=0.009), and the group with the lowest adiponectin level presented a 2.8 times higher risk of recurrence (1.03–7.68), even after adjusted by BMI and HOWA-IR. The metabolic syndrome, when evaluated in the negative HR patients group, was associated with a higher recurrence of breast cancer. However, this association fades after adjustment for the HOWA-IR and adiponectin variables. Leptin was not associated with prognosis factor for recurrence in this study.

In Europe, the study by Mantzoros et al.[19], of case-control nature, evaluated women with breast cancer (174 cases) and healthy women (167 controls), correlating measures of adiponectin, leptin, insulin-like growth factor 1 (IGF-1) and IGF bound to protein factor 3 (IGFBP-3). The study found a significant inverse association of breast cancer risk in the premenopausal period with levels of IGF-1 and IGFBP-3 (p=0.06 and 0.01, respectively), but not in the postmenopausal one. Leptin had no significant association with the risk of breast cancer in neither the pre- nor the postmenopausal period. There was significant association of low levels of adiponectin and increased risk of breast cancer in the postmenopausal period (OR=0.81; 95%CI 0.68–1.27; p=0.02).

The study by Macis et al.[20] exclusively included premenopausal women who had an increased risk of breast cancer or diagnosis of *in situ* or micro-invasive breast cancer, comparing four different chemoprevention groups with tamoxifen or placebo, with the objective of evaluating the recurrence of breast cancer and calculating the disease-free survival (DFS) in these groups. The levels of adiponectin and leptin were analyzed, as well as the leptin/adiponectin relation, IGF-1, glucose, insulin and insulin sensitivity by the HOWA criteria, related to the covariables of BMI and mammographic density percentage. Women with *in situ* and micro-invasive neoplasia

had significantly low adiponectin levels, and the leptin/adiponectin relation was significantly higher. Serum adiponectin levels were significantly lower, and the leptin/adiponectin relation was significantly higher in patients who experienced new events, while high serum adiponectin levels reduced the events (HR=0.87; 95%CI 0.79–0.95) of intraepithelial neoplasia and breast cancer by 8%, for each statistically significant increase in the adiponectin unit. The association of adiponectin with reduced risk of breast cancer in women was independent of BMI and the percentage of mammographic density. There was significant association, statistically significant (p=0.02), of adiponectin levels with DFS.

Cust et al.[21] carried out a case-control study with 1,121 women, evaluating the relation between BMI, levels of leptin, adiponectin, glycosylated hemoglobin (HbA1c) and CRP with risk of breast cancer. There was no association between BMI, levels of leptin, adiponectin, HbA1c and CRP with risk of breast cancer adjusted by age (≤55 years of age or less than 55 years of age), as well as their HR status. The study displayed a positive association between BMI, leptin and HbA1c with greater risk of breast cancer related to staging of the disease. For stage I, the highest and lowest leptin strata had an inverse relation with the risk of breast cancer (OR=0.45; 95%CI 0.22–0.91; p=0.03). There was a trend in stages II to IV of increased risk of breast cancer related to the highest and lowest strata of BMI (OR=1.89; 95%CI 0.99–3.59; p=0.05) and HbA1c (OR=1.91; 95%CI 1.00–3.66; p=0.05), although not significant to leptin (OR=1.39; 95%CI 0.65–2.96; p=0.40).

The study by Korner et al.[22] evaluated the levels of adiponectin, leptin and insulin and the expression of adiponectin receptors (Adipo R1/R2) in tumor tissue in women diagnosed with breast cancer. The study showed that women with higher adiponectin levels had a statistically significant reduction of 65% in the risk of death by breast cancer, regardless of the variables — age, BMI, reproductive and hormonal (estrogen) factors. Premenopausal and obese women were more prone to this benefit when compared to postmenopausal and non-obese women. Still in this study, the *in vitro* evaluation of adiponectin effects in normal and neoplastic cells cultures demonstrated that the exposure of breast cancer cells with positive estrogen receptors to adiponectin inhibited proliferation in 86% of malignant cells in the samples, in comparison to only 10% inhibition in normal cells.

The case-control study on postmenopausal women (875 cases and 839 controls)[23] in the United States had the objective of evaluating the role of adipokines along with inflammatory markers in the development of breast cancer. The study did not show any statistically significant association between adiponectin, leptin, resistin and inflammatory markers such as IL-6, TNFa and CRP with risk of breast cancer, in adjusted models. There was association between the reduced risk of breast cancer in high-level

serum quartiles (OR=0.76; 95%CI 0.59–1.12; p=0.06) for serum adiponectin levels, but this association was not significant in a multivariable analysis including insulin levels (OR=0.81; 95%CI 0.59–1.12; p=0.222). The CRP levels varied among patients who did and who did not undergo hormone replacement therapy (HRT), which reflected on the relation with the risk of breast cancer. Among patients who underwent HRT, the high levels of CRP was not related to the increased risk of breast cancer (OR=0.90; 95%CI 0.53–1.53; p=0.509); on the other hand, among patient who did not undergo HRT, the elevated levels of CRP correlated with the increased risk of breast cancer (OR=1.98; 95%CI 1.25–3.13; p=0.003) and maintained a significant positive association, even after adjusted in multivariate analysis[23].

Tworoger et al.[24] conducted a case-control study with 3,673 women with the objective of evaluating the association between serum adiponectin levels and the overall and menopausal risk of breast cancer. The study did not find any association between adiponectin levels and overall breast cancer, though it did observe a significant slight association to the menopausal status (p=0.008) between the highest and lowest serum adiponectin quartiles. This risk was of HR=1.3 (95%CI 0.80–2.10; p=0.09) in the premenopausal period; and HR=0.73 (95%CI 0.55–0.98; p=0.08) in the postmenopausal one, adjusted to the variables BMI, age, IGF-1 and IGFBP-1 levels. There was no difference between the adiponectin levels and the development of *in situ* or invasive cancer and HR expression in cancer. The study observed a non-statistically significant inverse relation between adiponectin levels and the risk of postmenopausal breast cancer, which was independent of estrogen levels and was maintained after adjusting the covariates for insulin resistance markers (C-peptide), IGF-1 and IGFBP-1[24].

Harris et al.[25] carried out a case-control study with 936 women evaluating the association of serum leptin levels and the risk of breast cancer. Association was observed between the levels of leptin and unadjusted breast cancer levels between the highest and lowest quartiles of serum leptin level (OR=0.66; 95%CI 0.40–0.96; p=0.05) and between leptin and breast cancer levels adjusted by the BMI (OR=0.55; 95%CI 0.31–0.99). The author concluded that the study demonstrated a significant borderline association between serum leptin levels in the largest quartile and the risk of breast cancer, although, after adjusted by the BMI model, there was no significance (p=0.26).

A cohort of 1,183 American women diagnosed with breast cancer and with doses of adiponectin, leptin, fasting plasma glucose and insulin was evaluated for mortality due to overall cancer and to breast cancer[26]. The study showed that serum adiponectin levels inversely correlated with HOWA-IR, BMI and leptin; more elevated levels of adiponectin reduced mortality due to breast cancer by 61%, and there was a positive association with survival. The HOWA-IR insulin resistance marker was associated to increased overall mortality, and the relation with

breast cancer mortality and in overweight women was more evident in higher quartiles. The study concluded by demonstrating the importance of the role of hyperinsulinemia as an independent factor of worst prognosis for women diagnosed with breast cancer and their association with low levels of adiponectin and shorter survival to breast cancer.

Gross et al.[27] conducted a case-control study on women with postmenopausal breast cancer correlated with BMI, levels of serum leptin, adiponectin and tumor necrosis factor receptor (TNF-R2) evaluated with the risk of breast cancer. The study showed that the cases had significantly higher BMI, serum leptin and TNF-R2 levels, in relation to the control group. Elevated levels of leptin and TNF-R2 were significantly related to a higher risk of breast cancer; the relation between high quartiles and low leptin level had OR=2.44 (95%CI 1.30–4.58; p=0.05), and low adiponectin levels were significantly related to the increased risk of breast cancer (OR=1.63; 95%CI 1.02–2.60; p=0.08). The high TNF-R2 inflammatory level (comparing the highest quartile to the lowest TNF-R2 serum level) was the strongest association factor with the risk of breast cancer (OR=2.44; 95%CI 1.30–4.58), with a significant response dose between the highest levels and the risk of breast cancer (p=0.008).

The Canadian study by Goodwin et al.[28] evaluated leptin levels in the breast cancer prognosis of 520 women. Women with stage I to III breast cancer had their leptin, blood glucose and insulin levels collected and followed prospectively, with the objective of evaluating leptin as a prognosis factor and their relationship with the survival rates of these patients. The results showed that the leptin was strongly correlated with BMI and serum insulin levels. Higher leptin levels were pointed out as factor of worse tumor prognosis: larger tumor size (p=0.0050), high histological grade (p=0.0023) and negative HR (for estrogen p=0.0470 and progesterone p=0.0023 receptors). There was no association of leptin levels with distant disease-free survival (DDFS) (HR=1.58; 95%CI 0.90–2.79) and risk of distant recurrence (HR=1.41; 95%CI 0.85–2.35; p=0.19). The association with worse overall survival (OS) was non-significant (HR=1.92; 95%CI 1.00–3.69; p=0.049), more evident in the postmenopausal period. In this same cohort of Canadian women, in a 12-year follow-up[29], variables related to insulin resistance (fasting insulin, HOWA-IR empirical estimate of insulin resistance, fasting glucose and peptide-C), to obesity (BMI, waist-hip ratio) and to serum leptin dosage in women with diagnosis of breast cancer were evaluated. The study showed a strong prognostic linear association with a worse prognosis in relation to DDFS and OS, in the first five years of breast cancer, with statistically significant factors related to insulin resistance. The BMI and serum leptin levels, in a univariate analysis, were significantly associated with prognosis in breast cancer[29].

DISCUSSION AND CONCLUSION

The epidemiological studies included in this review showed association between breast cancer and adipokines levels (adiponectin and leptin) and their prognostic relationship with one another. The studies which correlated adiponectin and leptin levels with BMI demonstrated inverse adiponectin relation and direct leptin one with this variable[16,20,21,26,28], and were consistent in assigning lower serum adiponectin levels to an increased risk of breast cancer among women in general — and in the postmenopausal period[15,16,24,25] —, regardless of BMI and variables related to insulin resistance markers. Two recent meta-analyses, by Macis et al.[30] and Liu et al.[31], evaluating the relation of serum adiponectin levels alone with the risk of breast cancer, had divergent results. The first one[30] showed inverse association between adiponectin levels and the risk of breast cancer, detecting 34% risk reduction for higher levels of serum adiponectin in general, in the postmenopausal period and in the premenopausal one. The later one[31] does not suggest association of adiponectin levels with breast cancer among women in general, although, in a subgroup analysis, there would be evidence of inverse association between serum adiponectin levels and the risk of breast cancer among postmenopausal women.

The quantification of serum adiponectin levels was correlated with differences in the risk of breast cancer: the lower the serum adiponectin levels, the higher the risks of breast cancer[15-17,19]. These findings have also been demonstrated in the meta-analysis by Ye et al.[32], which showed association of significantly lower levels of adiponectin and higher risk of breast cancer.

The studies by Korner et al.[22] and Duggan et al.[26], which evaluated the role of adiponectin in breast cancer prognosis, showed the relation of higher serum adiponectin levels with a better prognosis. In the study by Korner et al.[22], positive estrogen receptor cancer cells, when exposed to adiponectin, had inhibition of malignant cell proliferation as a response in 86% of the samples, compared to only 10% of inhibition effect on normal cells. The inhibition effect of tumor cell growth and the stimulation of apoptosis pathways by adiponectin in breast cancer tumor cells were observed in other *in vitro* studies, and in negative and positive HR tumor cells samples[32,33].

Although there is no consensus on the relation of high serum leptin levels and increased risk of breast cancer — as is the case of adiponectin —, studies demonstrated a positive correlation of high serum leptin levels with high BMI and insulin resistance parameters in patient with breast cancer — when compared to control ones[20,21,28]; and the relation of significantly high leptin/adiponectin in cases of breast cancer compared to healthy control ones[20]. The relation between serum leptin levels and the greater expression of their OB-R receptor (leptin) in larger breast cancer tissue samples was also related to a worse prognosis of the disease, translated into larger tumors and more advanced staging at diagnosis, as well as by the difference in recurrence and survival[34].

Serum leptin levels are representative of body fat mass: the serum leptin concentration increases in obesity and decreases during fasting. Adiponectin is reduced in obesity and in insulin resistance cases and increases in response to weight loss[35]. Low adiponectin levels are related to dyslipidemia, regardless of conditions of peripheral resistance to insulin and chronic inflammation[36]. Some studies have shown that the adiponectin stimulates peripheral tissue sensitivity to insulin, and the decreased serum levels would be related to an increase in serum insulin and peripheral insulin resistance parameters[37]. The study by Oh et al.[18] concluded that serum adiponectin levels may have a prognostic effect on patients with negative HR breast cancer, regardless of obesity and insulin resistance, postulating that adiponectin may be the connection between obesity, hyperinsulinemia and insulin resistance in the development and progression of breast cancer.

The heterogeneity of the studies and their results indicate there is probably no single stimulation pathway associated to a risk factor or prognosis that directs the onset of breast cancer and determines their biological behavior[23]. Hyperinsulinemia in obesity may or may not be associated to a diabetes mellitus (DM) diagnosis; studies are controversial in trying to establish the role of DM, increasing the risk of breast cancer[38]. Some studies evaluated the impact of Metformin use in the reduction of peripheral insulin resistance, impacting the reduction of risk and improving the prognosis of breast cancer, though with still contradictory results[39]. A more recent study by Calip et al.[40], with 10,050 diabetic women in treatment, did not detect, in a multivariate analysis adjusted for confounding factors with BMI, any decrease in the risk of breast cancer among patients using Metformin.

The adipose tissue is an active endocrine organ, which among other function secretes biomarkers, such as adipokines (adiponectin and leptin), involved in cancer activation pathways and proliferation. Epidemiological studies show that the metabolic dysregulation of obese patients with breast cancer, both in pre- and postmenopausal periods, expressed by low serum adiponectin and high serum leptin levels, increases the risk of breast cancer in patients with low adiponectin levels and worsens their prognosis, reducing the survival of patients with high serum leptin levels and low adiponectin ones. However, the metabolic dysregulation relation to unbalanced adipokines levels is not a single pathway for stimulation and progression of cancer. The interaction of the pathways related to insulin resistance and inflammation, to which the role of adipokines is associated, contributes or determines the development of breast cancer in women.

REFERENCES

1. World Health Organization. Burden of Cancer. National Cancer Control Programs. Policies and Managerial guidelines. Geneva: WHO; 2002. p. 17-21.

2. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371:569-78.

3. Pajares B, Póllan M, Martin M, Mackey JR, Lluch A, Gavila J, et al. Obesity and survival in operable breast cancer patients treated with adjuvant anthracyclines and taxanes according to pathological subtypes: a pooled analysis. Br Cancer Res. 2013;15(6):R105.

4. Chan DMS, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernam A, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol. 2014;25:1901-14.

5. Key T, Appleby P, Barnes I, Reeves G. Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Nat Cancer Inst. 2002;94:606-16.

6. Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer: a review of current evidence. Endocrine Review. 2012;33(4):547-94.

7. Nalabolu MR, Palasamudran R, Jamil K. Adiponectina e Leptina actions and clinical significances in breast cancer. Int J Hemato-Oncol Stem Cell Res. 2014;8(1):31-40.

8. Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of the withe adipose tissue. Brit J Nutrit. 2004;92:347-55.

9. Gulchelik MA, Colakoglu K, Dincer H, Dogan L, Yenidogan E, et al. Associations between adiponectin and two different cancers: breast and colon. Asian Pac J Cancer Prev. 2012;13(1):395-8.

10. Petridou E, Mantzoros C, Dessypris N, Kououlomatis P, Addy C, Vougaris Z, et al. Plasma adiponectin concentrations in relation to endometrial cancer: a case control study in Greece. J Clin Endocrinol Metabol. 2003;88:993-7.

11. Cirillo D, Rachiglio AM, La Montagna R, Giordano A, Normanno N. Leptin signaling in breast cancer: an overview. J Cell Biochem. 2008;105:956-64.

12. Giordano C, Chemi F, Panza S, Barone I, Bonofiglio D, Lanzino M, et al. Leptin as a mediator of tumor-stromal interactions promotes breast cancer stem cell activity. Oncotarget. 2016;7(2):1262-75.

13. Surmacz E. Leptin and adiponectin: emerging therapeutic targets in breast cancer. J Mammary Gland Biol Neoplasia. 2013;18(3):321-32.

14. Moher D, Liberati A, Tetzlaff J, Altaman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.

15. Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, Matsuzawa Y, et al. Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res. 2003;9:5699-704.

16. Tian Y, Chu C, Wu M, Chang C, Yang T, Chou Y, et al. Anthropometric measures, plasma adiponectin, and breast cancer risk. Endocr Relat Cancer. 2007;14:669-77.

17. Minatoya M, Kutomi G, Shima H, Asakura S, Otoozama S, Ohnishi H, et al. Relation of Serum Adiponectin Levels and Obesity with Breast Cancer: A Japanese Case-Control Study. Asian Pac J Cancer Prev. 2014;15(19):8325-30.

18. Oh SW, Park C-Y, Lee ES, Yoon YS, Lee ES, Park SS, et al. Adipokines, insulin resistance, metabolic syndrome, and breast cancer recurrence: a cohort study. Br Cancer Res. 2011;13:R34.

19. Mantzoros C, Petridou E, Dessypris N, Chavelas C, Dalamaga M, Alexe DM, et al. Adiponectin and breast cancer risk. J Clin Endocrinol Metab. 2004;89:1102-7.

20. Macis D, Gandini S, Guerrieri-Gonzaga A, Johansson H, Magni P, Ruscica M, et al. Prognostic Effect of Circulating Adiponectin in a Randomized 2 x 2 Trial of Low-Dose Tamoxifen and Fenretinide in Premenopausal Women at Risk for Breast Cancer. J Clin Oncol. 2012;30:151-7.

21. Cust AE, Stocks T, Lukanova A, Lundin E, Hallmans G, Kaaks R, et al. The influence of overweight and insulin resistance on breast cancer risk and tumour stage at diagnosis: A prospective study. Br Cancer Res Treat. 2008;113(3):567-76.

22. Korner A, Pazaitou-Panayiotou K, Kelesidis T, Kelesidis I, Williams CJ, Kaprara A, et al. Total and High-Molecular-Weight Adiponectin in Breast Cancer: In Vitro and in Vivo Studies. J Clin Endocrinol Metab. 2007;92(3):1041-8.

23. Gunter MC, Wang T, Cushman M, Xue X, Wassertheil-Smoller S, Strickler HD, et al. Circulating Adipokines and Inflammatory Markers and Postmenopausal Breast Cancer Risk. J Nat Cancer Inst. 2015;107(9):djv169.

24. Tworoger SS, Eliassen AH, Kelesidis T, Colditz GA, Willett WC, Mantzoros CS, et al. Plasma adiponectin concentrations and risk of incident breast cancer. J Clin Endocrinol Metabol. 2007;92(4):1510-6.

25. Harris R, Tworoger S, Hankinson SE, Rosner BA, Michels KB. Plasma Leptin Levels and Risk of Breast Cancer in Premenopausal Women. Cancer Prev Res. 2011;4(9):1449-56.

26. Duggan C, Irmin ML, Xiao L, Henderson KD, Smith AW, Baumgartner RN, et al. Associations of Insulin Resistance and Adiponectin with Mortality in Women With Breast Cancer. J Clin Oncol. 2011;29:32-9.

27. Gross AL, Newschaffer CJ, Hoffman-Bolton J, Rifai N, Visvanathan K. Adipocytokines, Inflammation, and Breast Cancer Risk in Postmenopausal Women: A prospective study. Cancer Epid Biom Prev. 2013;22(7):1319-24.

28. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, et al. Fasting insulin and outcome in early-stage breast cancer: Results of a prospective cohort study. J Clin Oncol. 2012;20(1):42-51.

29. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Taylor SK, et al. Insulin- and obesity-related variables in early-stage breast cancer: correlations and time course of prognostic association. J Clin Oncol. 2012;30(2):164-71.

30. Macis D, Guerrieri-Gonzaga A, Gandini S. Circulating adiponectin and breast cancer risk: a systematic review and meta-analysis. Int J Epidemiol. 2014;43(4):1226-36.

31. Liu L-Y, Wang M, Ma Z-B, Yu L-X, Zhang Q, Gao D-Z, et al. The Role of Adiponectin in Breast Cancer: A Meta-Analysis. PLoS One. 2013;8(8):e73183.

32. Ye J, Jia J, Dong S, Zhang C, Yu S, Li L, et al. Circulating adiponectin levels and the risk of breast cancer: a meta-analysis. Eur J Cancer Prev. 2014;23(3):158-65.

33. Dieudonne MN, Bussiere M, Santos E, Leveneu MC, Giudicelli Y, Pecquery R. Adiponectin mediates antiproliferative and apoptotic responses in human MCF7 breast cancer cells. Biochem Bioph Res Commun. 2006;345:271-9.

34. Ishiawa M, Kitayama J, Nagawa H. Enhanced expression of leptina and leptina receptor (OB-R) in human breast cancer. Clin Cancer Res. 2004;10(13):4325-31.

35. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin in obesity. Biochem Biophys Res Commun. 1999;257(1):79-83.

36. Von Eynatten M, Schneider JG, Humpert PM, Rudofsky G, Schmidt N, Barosch P, et al. Decreased plasma lipoprotein lipase in hypoadiponectinemia: an association independent of systemic inflammation and insulin resistance. Diabetes Care. 2004;27(12):2925-9.

37. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia. 2003;46:459-69.

38. Liao S, Li J, Wei W, Wang L, Zhang Y, Li J, et al. Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. Asian Pac J Cancer Prev. 2011;12:1061-5.

39. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CS. Long-term Metformin use in associated with decreased risk of breast cancer. Diab Care. 2010;33(6):1304-8.

40. Calip GS, Yu O, Elmore JG, Boudreau DM. Comparative safety of diabetes medications and risk of incident invasive breast cancer: a population-based cohort study. Cancer Cause Control. 2016;27(5):709-20.

THE STANDARDIZATON OF PHOTOGRAPHIC RECORDS FOR ONCOPLASTIC AND BREAST RECONSTRUCTIVE SURGERY

Padronização do registro fotográfico das pacientes submetidas à cirurgia oncoplástica e reconstrutiva da mama

Paula Cristina Martins Soares[1]*, Douglas de Miranda Pires[2], Cristina Maria de Medeiros[3]

ABSTRACT

Medical photography is an important diagnostic logging tool, since it allows pre-and postoperative comparisons to be made and it disseminates knowledge to the scientific community. The evolution of digital imaging has made the use of cameras easier and has increased access to better quality equipment. Photography is an essential tool in dermatologists' and plastic surgeons' practices. Breast surgeons' recent acquisition of oncoplastic surgical techniques, reconstructive and breast remodeling surgery has led to the need for photographic records in the area. This photographic registration reproduces reality with maximum details and relevant information, as it follows a standardized way of positioning, backgrounds and photographic angles. This study aims to recommend the most appropriate camera, conduct basic equipment adjustments and standardize photographic records of patients undergoing reconstructive and oncoplastic breast surgery. A literature review was conducted in the Cochrane Library, Scielo Brazil, PubMed and Google.

KEYWORDS: Photography; breast; plastic surgery; mammoplasty.

RESUMO

A fotografia médica é uma importante ferramenta de registro, permitindo a comparação pré e pós-operatória, bem como a transmissão de experiência à comunidade científica. A evolução da fotografia digital facilitou o uso de câmeras fotográficas e favoreceu o acesso a equipamentos de melhor qualidade. Os dermatologistas e cirurgiões plásticos tradicionalmente utilizam a fotografia na prática clínica diária. Com a recente incorporação de técnicas cirúrgicas de oncoplastia, cirurgia reconstrutiva e remodelamento mamário, constata-se a importância da prática do registro fotográfico na mastologia. Esse registro deve reproduzir a realidade com o máximo de detalhes e informações relevantes, seguindo a padronização de posições, fundo e ângulos fotográficos. Este estudo visa sugerir a escolha da câmera fotográfica, orientar regulagens básicas do equipamento e padronizar o registro fotográfico das pacientes que serão submetidas à cirurgia oncoplástica e reconstrutiva da mama. Foi realizada revisão bibliográfica na Cochrane, Scielo Brasil, PubMed e Google.

PALAVRAS-CHAVE: Fotografia; mama; cirurgia plástica; mamoplastia.

INTRODUCTION

Since its emergence in the first half of the nineteenth century, photography has become an important tool for registration in several scientific fields. The field of medicine quickly incorporated this image producing technique, since it is far superior to drawings, due to its wealth of details and fidelity to reality. With cameras, it was possible to register patients, surgical procedures, cells and tumors[1].

Artistic photography incorporates sophisticated techniques of laboratory or studio lighting effects. On the other hand, medical photography should reproduce reality with the maximum number of details and relevant information possible, and it should follow a standardized way of positioning, backgrounds and photographic angles[2-4]. It is an important diagnostic logging tool, which allows for pre-and postoperative comparisons and the dissemination of knowledge to the scientific community. The evolution of digital imaging has made camera use easier and has increased access to better quality equipment. Surgeons' recent acquisition of oncoplastic surgical techniques and reconstructive and breast remodeling surgery has led to the need for photographic records.

CHOOSING A CAMERA

When choosing a camera it is important to consider four main factors: resolution, convenience, creative control and cost[5]. After the introduction of digital technology in the 1980's, photography has had rapid development[6]. The cost of a camera has decreased and there is a great diversity of models available, which makes access to such equipment easier. Camera cost is usually directly proportional to quality, technology, and optional controls.

Regardless of the choice of equipment, a camera is only a tool. With a basic knowledge of photographic techniques, a surgeon can take great pictures of patients[6].

Types of cameras

Most compact cameras are typically point-and-shoot and have all automatic adjustments. Some more complex models have commands that enable their use in different conditions: portrait, landscape, night, close up, etc.[5]. These cameras do not allow the exchange of lenses and they have small sensors, which limits their use and the quality of the image. They require simpler handling procedures, and are lighter and cheaper.

D-SLR (digital single-lens reflex) cameras are for professional and semi-professional use. With them, the image is reflected by a mirror directly to a display instead of being captured by a sensor. Therefore, the image can be reproduced on an LCD screen behind the camera[5]. When a picture is taken, this mirror is collected and the sensor captures the image. D-SLR cameras allow for an exchange of lenses and they have many creative commands, which increases their range of use. They have larger sensors and better technology, and thus generate better quality images. They are bigger, heavier and more difficult to use. Additionally, they have a higher cost.

In the past few years, the industry created so-called micro system cameras or mirror-less cameras, which make up an intermediate category between compact and D-SLR. They combine the advantages of compact cameras (small and lightweight) and the advantages of reflex cameras (large sensors, the possibility to exchange lenses, and great quality images)[6]. They are not as expensive and are more convenient to carry in your daily purse. The latest models have bluetooth technology, which allows pictures to be transmitted to phones, tablets or computers without the use of cables, for easy archiving.

For surgeons that are beginners in photography, the use of a mirror-less camera is suggested, due to the previously mentioned advantages. For lovers and scholars of photographic techniques, D-SLR cameras are the best option.

Digital image resolution

The digital camera image is made as a sensor captures light, and is composed of millions of tiny elements, pixels. A pixel is the smallest point that forms a digital image. The word *pixel* is based on a contraction of *pix* from the word "pictures" and *el* for "element".

The number of pixels (measured in millions or megapixels-mp) influences the image magnification possibilities. A 15×10 cm photo needs 2 mp to be printed with excellent quality and a 28×35 cm photo requires 6 mp[5].

The number of megapixels a camera has does not determine image quality. Sensor size should be considered instead. The higher the camera sensor, the better the image quality[7].

There are now two types of sensors available: the CCD (charged-coupled device) and the CMOS (complementary metal-oxide semiconductor). The latter is more common in D-SLR cameras, while the CCD equip compact ones[5,6].

A camera that has a 3 to 6 megapixel resolution is suitable for the photographic record proposed for breast surgery[8].

CAMERA ADJUSTMENTS

The basics of photographic techniques

The "photographic triangle" is composed by the aperture, shutter speed and ISO (International Standard Organization)[6]. The congruence among these factors produces a good quality photo (Figure 1). The focal length, coverage angle and white balance should also be noted.

Digital cameras have automatic control for these parameters. But knowledge of adjustments allows you to improve image quality and correct errors that are not identified by the equipment[6].

Exposure: aperture and shutter speed

In photography, exposure means the amount of light that falls onto the digital camera sensor, which is controlled by the balance between aperture and shutter speed.

The aperture is a small set of blades in the lens and it controls how much light will enter the camera[5] (Figure 2). The blades create an octagonal shape that can be widened or shrunken down to a small hole. Aperture size is measured by *f-stops*. A high *f-stop* like *f*-22 means that the aperture hole is quite small and a low *f-stop* like *f*-3.5 means that the aperture is wide open. An analogy for aperture is the iris of an eye[6].

The shutter is a mechanical device that opens and closes, and controls the amount of time the sensor is exposed to light[5]. It would be like the camera's eyelids, and its movement is similar to blinking[6]. It is measured in fractions of a second. A normal shutter speed is around 1/125th of a second with a standard lens or mid-range zoom lens on the camera. Unless you have extremely shaky hands, this will give you a sharp picture most of the time.

As the shutter opens, the movement of the scene is registered. Shorter shutter speed times record "frozen" scenes, like drops of water coming out of a faucet (1/500th sec). On the other hand, if the shutter is opened for a longer period of time, a "blurry" image is created, like the classic waterfall veil image (1/30th sec)[5,6]. At shutter speeds slower than 1/30th of a second, it is quite difficult to hold the camera steady enough to get a sharp image, and the use of a tripod is necessary.

International Standard Organization

The last part of the "photographic triangle" is the ISO (International Standard Organization), which represents the sensor's sensitivity to light, in the equivalence to ASA (American Standards Organization) of the old 35 mm films[5].
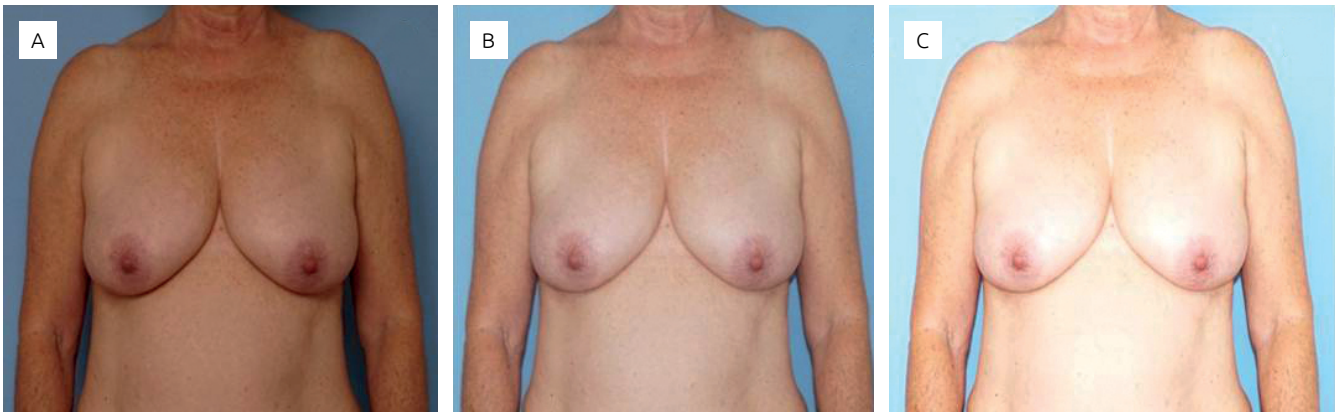

Photo: Paula Soares.
Figure 1. Exposure: A) dark photo; B) ideal photo; C) bright photo.

Photo: Cristina Medeiros.
Figure 2. Aperture sizes. Small aperture (*f*-22), less light strikes the image sensor. Large aperture (*f*-2.8), more light strikes the image sensor.

The ISO setting depends on the brightness of the space. In lighter rooms, ISO 100 must be selected, and in darker rooms, ISO 400 is preferred. When increasing the ISO above 400, the image can become grainy and lose its quality.

The ISO setting between 100 and 400 allows for good photographs in office environments[5,6].

Focal length

The measurement of focal length appears engraved on the body of the lens (Figure 3). Each lens has a coverage angle, which is the angle that the lens can capture the image. The shorter the focal length, the greater the coverage angle. A focal length of 14 mm has a coverage angle of 106° and a focal length of 135 mm has an angle of 18°.

A 50 mm lens is satisfactory for the use proposed by breast surgeons, as its angle of coverage is very similar to the central field of the human eye[8,9]. With this lens you can record images of the entire body or just the torso, which is the focus of interest for breast surgery.

White balance

Digital cameras can automatically correct different color temperatures by changing the white balance command (flash, sunlight, shade, fluorescent light, incandescent light). There are also manual settings to adjust incorrect assumptions from the automatic system[5] (Figure 4).

LIGHTING FOR PHOTOGRAPHY

Lighting has a fundamental role in photography. The ideal lighting when taking a patient's photo is that which registers the correct
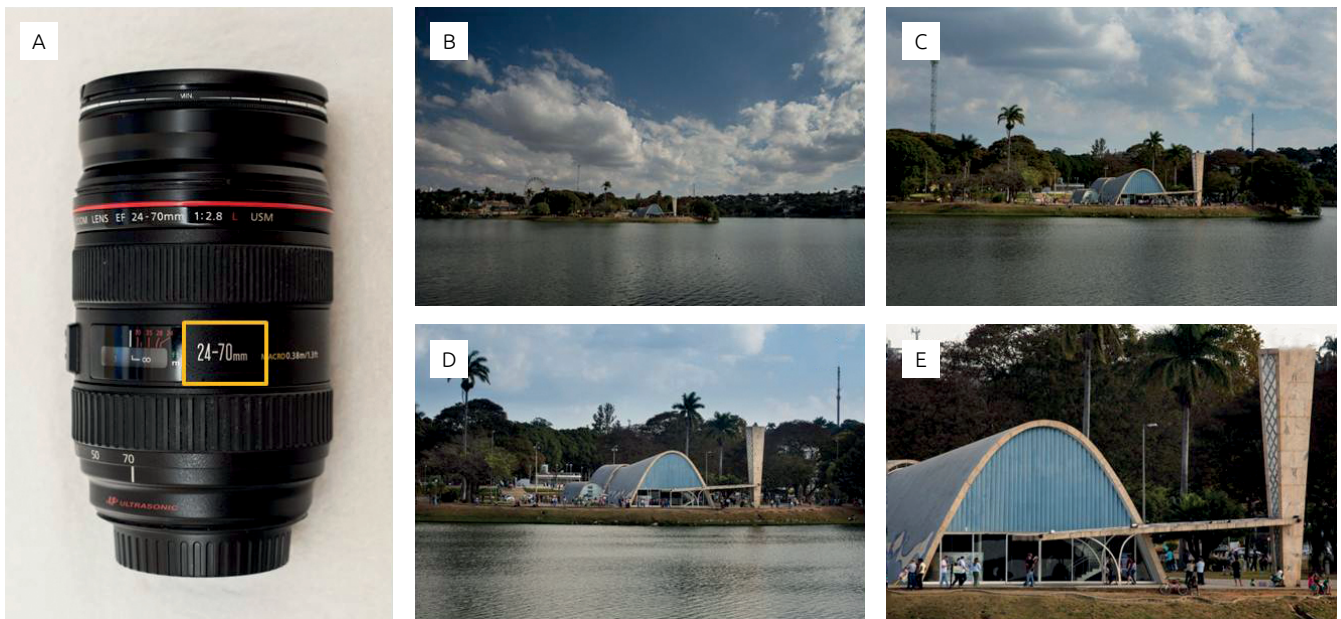

Photo: Cristina Medeiros

Figure 3. Focal length: A) Lens with focal length 24-70 mm; B–E) the same scene registered with different focal lengths (24, 70, 200 and 300 mm).
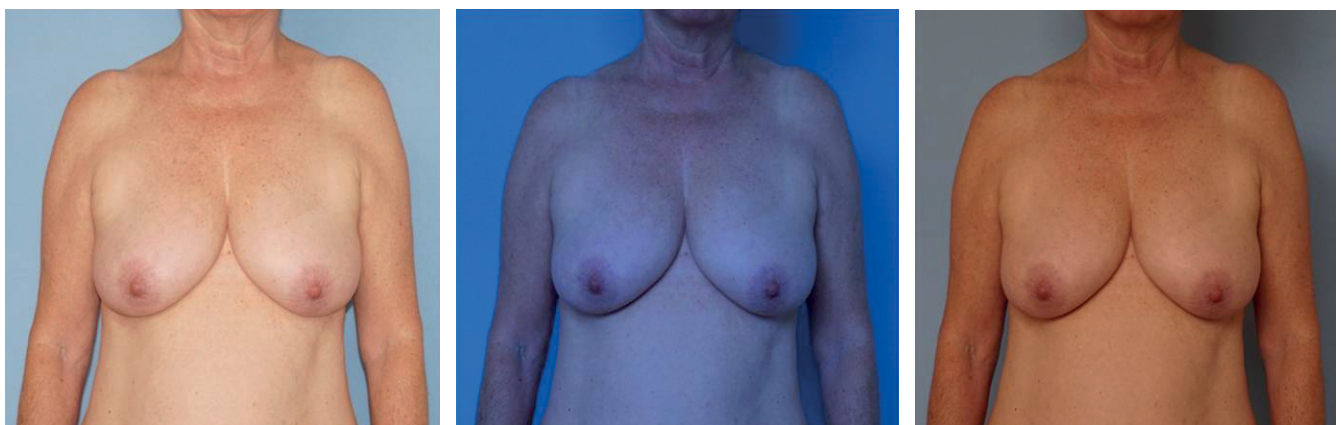

Photo: Paula Soares.

Figure 4. Differences in skin color and in the blue photographic background according to the white balance set in the camera.

skin color and the contours of the breast and the abdomen, which allows for a comparison of before and after the surgical procedure.

Different sources of light produce different colors, according to the Kelvin color temperature scale (Figure 5).

The natural light that enters through the window is very heterogeneous. It is more bluish at noon and more orange at the beginning and end of the day[6]. Artificial light can come from lamps on the ceiling or wall. Artificial lighting color varies with the type of bulb used. Tungsten light bulbs disperse orange light and fluorescent light bulbs have more of a bluish light. Led light bulbs can have different colors, which vary from warm white (2700-3500 k), neutral white (4000-4500 k) or cold white (5700-6500 k) (Figure 5).

In general, most exam rooms have sufficient lighting for clinical photography. Standard halogen or fluorescent light bulbs typically provide more than enough light, so long as the wattage of the bulbs is sufficient. Incandescent lights are not optimal for clinical photography, just as they are not optimal for an exam room.

Surgeons must observe the temperature color of the room light where photographs will be taken and be sure that the light is directed toward the area being photographed. The brain can adjust these variations, but to achieve proper lighting for photography, the camera must be set[6].

Light hardness and the use of a flash

Light hardness is defined by shadows that appear in the image, whether strong or mild (Figures 6A and 6B). Soft shadows are important for drawing volumes and contours of the torso and breast.
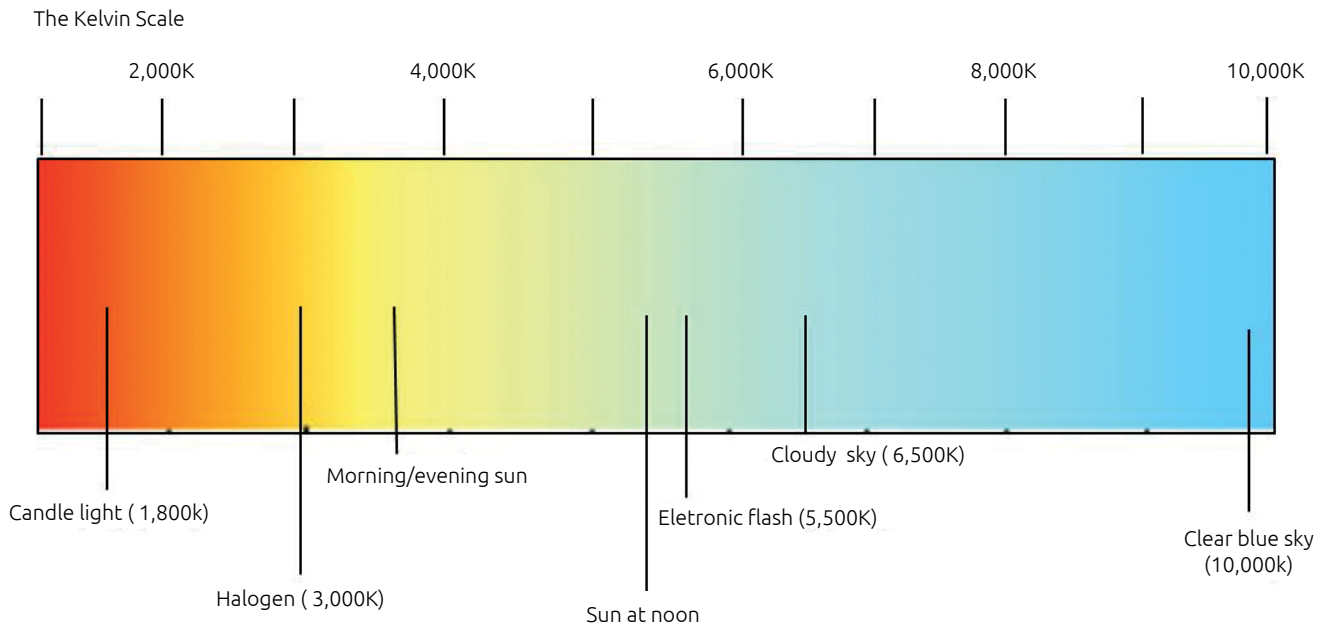

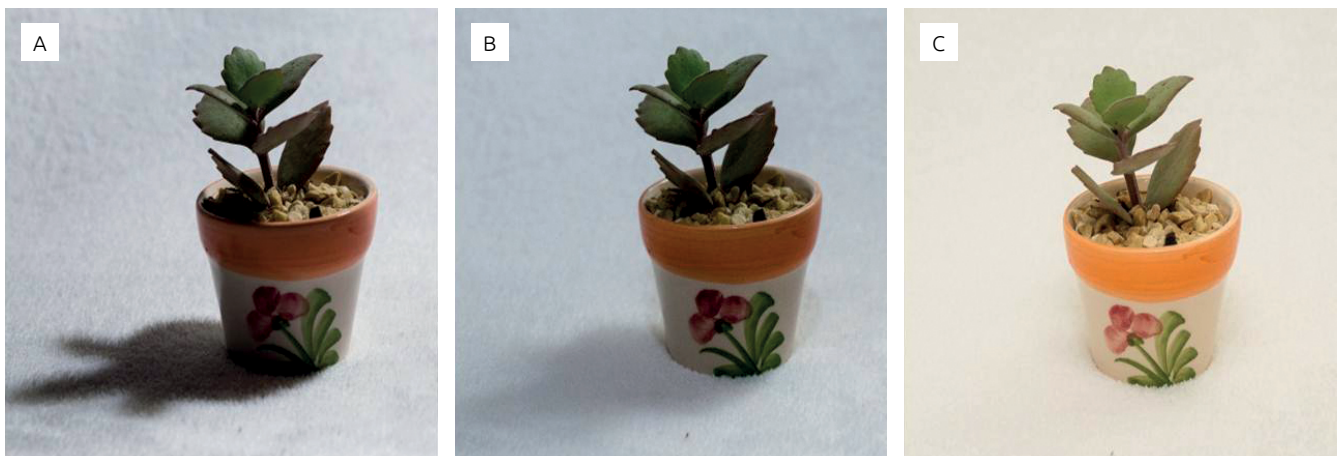**Figure 5.** The color temperature of the Kelvin Scale.

Figure 6. Light hardness: A) strong shadow or " hard light"; B) "soft light"; C) the use of a flash, bouncing light off the ceiling or walls, scattering the rays and creating more natural light.

"Soft light" is defined when shadows are nonexistent or are discreet, with subtle edges that allow you to view what is inside of them[9].

"Hard light" causes strong and marked shadows and hides features[9].

Using the flash

A flash is used to correct or supplement the ambient light, especially when the ambient light is insufficient or is distributed irregularly[5,6,8,9].

The in-camera flash produces lighting that is flat, which gives the impression that the subject has been run over by a steam-roller. It is usually limited, causing very strong sparkles and remarkable shadows ("hard light")[9]. When buying a camera, it is important to evaluate the possibility of attaching an external flash with a rotating head, which allows light to bounce off of the ceiling or walls, scattering the rays and creating more natural light or ideal "soft light"[6,9] (Figure 6C).

THE STANDARDIZATION OF PHOTOGRAPHS

For two photos to be comparable, it is necessary to maintain the same aperture, shutter speed, ISO, photographic background and, especially, the same patient positioning in both[3,6,7,10]. It is essential to establish a routine for taking photos that starts with the patients signing the informed consent form[3].

The patient must be clearly identified in the picture. The use of a label with name initials, birth and registration date is suggested. A second option is to capture the patient data in the first photo of the sequence[3,7].

When composing the picture, it is recommended that environmental elements like tables, chairs, pictures and doors be removed[7].

Patients should not use jewelry, clothing, scarves or glasses hung around the neck[7,9,10,11].

Background

The photographic background should be smooth, uniform and opaque to prevent reflections[7,8,10,12]. It is suggested to use a fabric, a painted wall or even a retractable non-reflective backdrop.

The accepted backdrops are white, black, green, gray or blue[7]. However the darker backgrounds can interfere with pictures of dark skinned people and the white background can interfere with the pictures of light skinned people.

According to the Clinical Photography Committee of the Plastic Surgery Educational Foundation, light to medium blue is a good choice because it contrasts well with all skin tones[8,10,11] (Figure 7). Medium gray may also work well[7]. Patients should stand 50 to 90 cm from the backdrop[10,12].

Patient positioning

In clinical photography, patients should be at the center of the frame and must fill most of the photo[8,11]. In mirror-less and D-SLR cameras, it is possible to include gridline bars in the preview screen. The gridlines are very helpful for getting the shot straight and allowing for the correct torso positioning in the frame center in both horizontal and vertical references[11,12] (Figure 7).

To make standardization easier, the use of stickers on the floor which mark the correct positioning of the patient's legs to the front, oblique and profile photos, as well as their distance from the camera and the photographic backdrop is recommended[8,11].

The camera must be positioned at the same height as the patient's breast[10,11]. Photos taken from bottom to top or from top to bottom, which distort the body image must be avoided.

For patients undergoing oncoplastic and reconstructive breast surgery, six photos are proposed: frontal, dorsal, right profile, left profile, right oblique view, left oblique view.

Frontal and dorsal view

The patient should stand comfortably erect with their arms at their sides. Their feet should be aligned with the appropriate tape marks on the floor[11].

Including the patient's abdomen in the frame is necessary in the photographic record for oncoplastic surgery, since it allows the possibility to evaluate the skin and adipose tissue available for breast reconstruction with the rectus abdominis myocutaneous flap. Similarly, the dorsal photo allows for the evaluation of the donor area to be used for breast reconstruction with the latissimus dorsi myocutaneous flap (Figure 8).

Oblique views

For oblique views, the distal arm should be moved back slightly[11,12]. Feet should be aligned with appropriate tape marks on the floor (Figure 8).
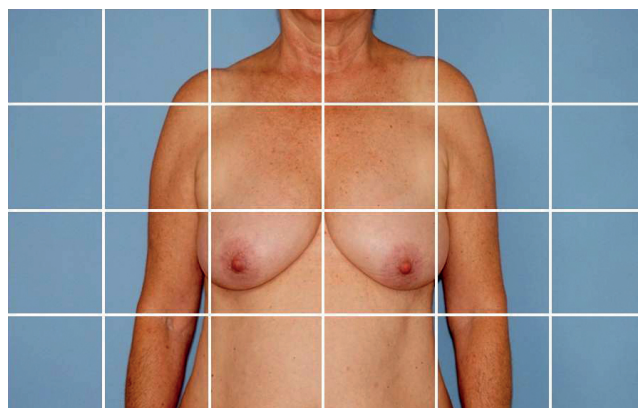
Fonte: Paula Soares.

Figure 7. Set the camera to show gridlines in the preview screen. They are very helpful for getting the shot straight, allowing the correct torso positioning in the center of the frame, and in horizontal and vertical references.
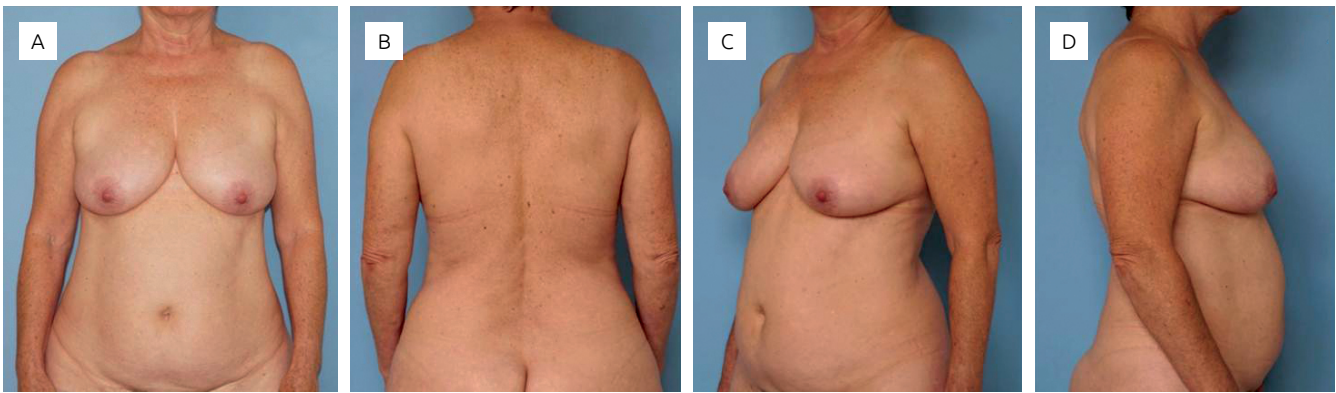
Photo: Paula Soares.

Figure 8. A) Frontal view: upper limit: ment; lower bound: pubic symphysis; B) dorsal view - upper limit: inferior nuchal line; lower bound: iliac crest; C) right and left oblique view. Upper limit: ment; lower bound: pubic symphysis; D) right and left lateral views. Upper limit: ment; lower bound: pubic symphysis.

Lateral views

In lateral views, the distal breast should not be visible[10-12].

CONCLUSION

Mastology is a medical specialty that has had continuous progress in the past two decades, both in genetics and molecular diagnostics and in incorporating oncoplastic surgical techniques. Good aesthetic results should be connected to oncologic treatment.

The photographic record of patients becomes a fundamental tool in clinical practice, allowing for decisions regarding surgical technique, pre-and postoperative comparisons, the registration of possible technical ability improvements for the staff, and the dissemination of knowledge to the scientific community.

REFERENCES

1. Costa FM. Cem anos de fotografia científica em Portugal (1839-1939). Lisboa: Edições 70; 2014.

2. Riml S, Piontke AT, Larcher L, Kompatscher P. Widespread disregard of photographic documentation standards in plastic surgery: a brief survey. Plast Reconstr Surg. 2010;126(5):274e-6.

3. Aveta A, Filoni A, Persichetti P. Digital Photography in Plastic Surgery: The importance of Standardization in the Era of Medicolegal Issues. Plast Reconstr Surg. 2012;130(3):490e-1e.

4. Paccanaro RC. Padronização e avaliação fotográfica em cirurgia periorbital. Rev Bras Cir Plást. 2010;25(2):278-84.

5. Hedgecoe J. O novo manual de fotografia: guia completo para todos os formatos. São Paulo: Senac; 2013.

6. Pinheiro MVB. A fotografia na cirurgia dermatológica e na cosmiatria – Parte 1. Surg Cosmet Dermatol. 2013;5(2):101-8.

7. Pinheiro MVB. Photography in surgical and cosmetic dermatology – Part II. Surg Cosmet Dermatol. 2013;5(3):189-98.

8. Hochman B, Nahas FX, Ferreira LM. Fotografia aplicada na pesquisa clinico-cirúrgica. Acta Cir Bras. 2005;20(Suppl. 2):19-25.

9. Stocchero IN, Torres FC. Fotografia digital em cirurgia plástica. São Paulo: Livraria Médica Paulista; 2005.

10. Persichetti P, Simone P, Langella M, Marangi GF, Carusi C. Digital Photography in Plastic Surgery: how to achieve reasonable Standardization outside a Photographic Studio. Aesthet Plast Surg. 2007;31(2):194-200.

11. The Plastic Surgery Educational Foundation, American Society of Plastic Surgeons. Photographic standards is Plastic Surgery. 2006.

12. Tobar SS, Vieira R, Chagas CR. Padrões fotográficos em mastologia. Rev Bras Mastologia. 2016;26(2):70-4.

BREAST NECROSIS IN A CHRONIC USER OF WARFARIN

Necrose mamária em usuária crônica de varfarina

Geraldo Antônio Cassol[1], Fabrício Farias Morales[2,3], Mariana Luz Stocco[2,3], Mariana Pimenta Pinheiro[2,3]*

ABSTRACT

A necrose cutânea induzida por varfarina é um evento raro, que geralmente ocorre nos primeiros dias de uso dessa medicação, sendo atribuída ao provável efeito inicial pró-trombótico causado pelo desbalanço transitório entre fatores pró e anticoagulantes. É descrito o primeiro caso de necrose mamária em uma mulher de 50 anos usuária crônica de varfarina, a qual teve seu efeito anticoagulante potencializado pelo uso concomitante de diclofenaco sódico.

PALAVRAS-CHAVE: necrose; mama; varfarina.

RESUMO

Warfarin-induced skin necrosis is a rare event that generally happens within the first days of warfarin use and is due to the initial, and transitory, prothrombotic state caused by unbalanced pro and anticoagulant factors. We describe the first case of breast necrosis in a 50-year-old woman, who uses warfarin chronically, and had its anticoagulant effect enhanced by the concomitant use of diclofenac.

KEYWORDS: necrosis; breast; warfarin.

INTRODUCTION

The use of warfarin has been associated with skin necrosis since the early 1940s. It is a rare event, with only a few cases described in the literature, occurring more often in the breasts, buttocks, and thighs. Its development is catastrophic, thus requiring early diagnosis and immediate intervention in order to reduce the morbidity and to prevent potential mortality and related complications.

CLINICAL CASE

This study reports a case covered by the Mastology team of the Health Department of the city of Joinville, Santa Catarina, Brazil. The informed consent was signed, and the patient agreed to the exposure of her medical conditions for scientific purposes.

The patient is a 50-year-old woman with body mass index (BMI) of 33.6, with hypertension — using amlodipine 10 mg/day — and pulmonary thromboembolism at age 33 — using warfarin 5 mg twice a week and 7.5 mg on the remaining days. She denied using alcohol, smoking or having allergies. Despite laboratory follow-up of the anticoagulation with the International Normalized Ratio (INR) maintained in the therapeutic range of 2.5–3.0, she presented popliteal venous thrombosis at the age of 44. An extensive thrombophilia research was carried out, which came out negative for protein C deficiency, S factor V Leiden, mutated prothrombin gene, lupus anticoagulant and anticardiolipin antibody. She reported that 10 days before admission, after working out at home, she took some diclofenac for muscle pain. Two days later, she developed a progressive pain in her right breast, with local erythema, without fever or any other associated symptom, and was then hospitalized. When admitted in the hospital, she was in good overall condition, her blood pressure was 130/90 mmHg, heart rate of 80 beats per minute, and she was afebrile. Her right breast had an ecchymotic area with predominant central distribution. Laboratory testing presented: hemoglobin = 12.3; hematocrit = 42; leukocytes = 9,600; platelets = 153,000; and INR = 8.

Warfarin was then discontinued, and frozen fresh plasma was administered. The patient reports that her breast pain continued worsening, evolving with quick hardening and blackening of the skin in the region, hence the diagnosis of extensive right breast necrosis (Figure 1). The patient underwent breast debridement, resulting in total mastectomy; a devitalized mammary tissue with superficial skin necrosis was observed during the intraoperative period. The anatomopathological analysis of the surgical specimen revealed extensive necrosis of coagulation with hemorrhagic areas, congestive vessels and capillaries, releasing a final report of gangrene.

DISCUSSION

Skin necrosis is a rare condition, with incidence of 0.1 to 0.01% of cases in users of oral anticoagulant therapy whose action mechanism is the antagonism of vitamin K[1-9]. Flood et al. described the condition for the first time in 1943[10], but a causal relation between tissue necrosis and use of oral anticoagulants was only established in the late 1950s[11]. Subsequently, an association between thrombophilia, warfarin use and skin thrombosis was established, which was described in patients with hereditary deficiency of protein C[12-14], deficiency of protein S[15], antithrombin III[16], V Leiden factor[17], and lupus anticoagulant carriers[18]. It was also described in patients requiring high initial doses of oral anticoagulant, higher than 10 mg of warfarin[2,3]. However, most cases occur without a predisposing risk factor or known cause.

The warfarin-induced skin necrosis usually occurs in areas of excessive subcutaneous cellular tissue, most frequently affecting breasts (10 to 15%)[19-22], buttocks, and thighs[23,24]. It typically occurs in obese middle-aged women, using warfarin due to deep venous thrombosis and/or pulmonary thromboembolism, and it is rare among coumarin users due to cerebrovascular insufficiency and atrial fibrillation[11]. The first signs appear in the period between the first week and 10 days after the beginning of warfarin use, with visual lesions between the third and sixth days[4,20]. Late cases developed after 16 days have already been described[7]. The onset of symptoms is characterized by paresthesia, or the sensation of a visceral, poorly located discomfort, which evolves with the appearance of painful, erythematous lesions with poorly defined margins that progress to ecchymotic areas. Edema of the subcutaneous cellular tissue occurs, resulting in an orange peel-like skin in the area[21], progressing into dry gangrene[4,21]. The anatomopathological substrate is an occlusive non-vasculitic vasculopathy[25].

Figure 1. Right breast necrosis.

The pathophysiology of the condition remains uncertain, but it is believed that in the beginning of oral anticoagulant whose action mechanism is vitamin K antagonism, there might be a transitory deficiency of proteins C and S, predominantly[26,27], as well as of factor VII (12-hour shorter half-life), which have faster drop in their concentrations than the other factors involved in pro-coagulation (factors II, IX, X), whose half-life is between 20 and 60 hours. Thus, there is a non-counterbalanced reduction of these proteins, resulting in a prothrombogenic period between the first 3 to 6 days, considering the peak of anticoagulant activity is only reached in 72 to 96 hours[28]. Therefore, the concomitant use of heparin is recommended in the initial phase[12]. Some authors also point out that the warfarin has a toxic effect on the pre-capillary and arteriolar junction of the dermis, causing the endothelial lesion[1,11].

The diagnosis is essentially clinical, and the histological aspect is characterized by skin infarcts with hemorrhage areas and rupture of pre-capillary arterioles with fibrin deposit and absence of perivascular inflammation, i.e., an occlusive, non-vasculitic vasculopathy[4,20,23,25].

In the case above, the patient was a chronic warfarin user, but who, due to the concomitant and erroneous use of diclofenac, experienced a potentialized coumarin effect, which was evidenced by larger INR at hospital admission; as a result, there was a transient imbalance between pro- and anticoagulant factors, generating a prothrombotic state that culminated in skin necrosis. It should be noted that the patient had already presented superficial popliteal thrombosis, considering the recurrence of venous thrombosis has also already been described during anticoagulant treatment with warfarin – incidence of up to 3 to 15% of cases[28].

The treatment of warfarin-induced breast necrosis, although not interfering with the progression of gangrene, should begin as early as possible in order to avoid related complications, such as secondary infections. It consists in the administration of low-molecular weight heparin doses enough for full anticoagulation, oral anticoagulant suspension, administration of fresh plasma and vitamin K, thus restoring proteins C and S through hepatic production stimulation[29]. The use of new oral anticoagulants with different action mechanism, such as direct thrombin inhibitors of the Xa factor, is also advocated[30]. Currently, despite proper treatment, more than half of the patients will require surgical debridement, amputation or total mastectomy[19-22,24,26,29].

REFERENCES

1. Schleicher SM, Fricker MP. Coumadin necrosis. Arch Dermatol. 1980;116:444-5.

2. Cole MS, Minifee PK, Wolma FJ. Coumarin necrosis: a review of the literature. Surgery. 1988;103:271-7.

3. Eby CS. Warfarin-induced skin necrosis. Hematol Oncol Clin North Am. 1993;7:1291-300.

4. Chan YC, Valenti D, Mansfield AO, Stansby G. Warfarin induced skin necrosis. B J Surg. 2000;87(3):266-72.

5. Moll S. Warfarin-induced skin necrosis. Br J Haematol. 2004 Sep;126(5):628.

6. Vu TT, Gooderham M. Adverse Drug Reactions and Cutaneous Manifestations Associated With Anticoagulation. J Cutan Med Surg. 2017 Jun 1:1203475417716364.

7. Xin C, Hu D, Li M. Late onset warfarin-induced skin necrosis, a case report. G Ital Dermatol Venereol. 2014 Nov 20.

8. Liaw TY, Chang CH. Skin necrosis complicated by warfarin-induced protein S deficiency. J Formos Med Assoc. 2014 Oct;113(10):758-9.

9. Harenberg J, Hoffmann U, Huhle G, Winkler M, Bayerl C. Cutaneous reactions to anticoagulants. Recognition and management. Am J Clin Dermatol. 2001;2:69-75.

10. Flood EP, Redish MH, Bociek SJ, Shapiro S. Thrombophlebitis migrans disseminate: report of a case in which gangrene of the breast occurred. Observations on the therapeutic use of dicumarol (3,3'methylenebis(4-hydroxycoumarin). N Y State J Med. 1943;43:1121-4.

11. Nalbandian RM, Mader IJ, Barrett JF, Pearce JF, Rupp EC. Petechiae, ecchymoses, and necrosis of skin induced by coumarin congeners. Rare, occasionally lethal complication of anticoagulant therapy. JAMA. 1965;192:603-8.

12. Dahlbäck B, Villoutreix BO. The anticoagulant protein C pathway. FEBS Lett. 2005;579(15):3310-6.

13. Gladson CL, Groncy P, Griffin JH. Coumarin necrosis, neonatal purpura fulminans, and protein C deficiency. Arch Dermatol. 1987;123:1701a-6a.

14. Lai J, Ramai D, Alchi R, Bloomfield D. Anticoagulation therapy for thromboembolism prevention: a case of warfarin-induced skin necrosis in the setting of protein C deficiency. BMJ Case Rep. 2017 May 12;2017.

15. Grimaudo V, Gueissaz F, Hauert J, Sarraj A, Kruithof EK, Bachmann F. Necrosis of skin induced by coumarin in a patient deficient in protein S. BMJ. 1989;298:233-4.

16. Kiehl R, Hellstern P, Wenzel E. Hereditary antithrombin III (AT III) deficiency and atypical localization of a coumarin necrosis. Thromb Res. 1987;45:191-3.

17. Dahlbäck B. New molecular insights into the genetics of thrombophilia. Resistance to activated protein C caused by Arg506 to Gln mutation in factor V as a pathogenic risk factor for venous thrombosis. Thromb Haemost. 1995;74:139-48.

18. Moreb J, Kitchens CS. Acquired functional protein S deficiency, cerebral venous thrombosis, and coumarin skin necrosis in association with antiphospholipid syndrome: report of two cases. Am J Med. 1989;87:207-10.

19. Kagan RJ, Glassford GH. Coumadin-induced breast necrosis. Am Surg. 1981;47(11):509-10.

20. López Valle CA, Hébert G. Warfarin-induced complete bilateral breast necrosis. Br J Plast Surg. 1992;45(8):606-9.

21. Khalid K. Warfarin-induced necrosis of the breast: case report. J Postgrad Med. 2004;50(4):268-9.

22. Ejzenberg D, Neusquen LP, Rolnik DL, Lozinsky AC, Piato JR. Breast necrosis induced by the use of coumadin: case report and review of literature. Einstein (Sao Paulo). 2015 Jul-Sep;13(3):417-9.

23. DeFranzo AJ, Marasco P, Argenta LC. Warfarin-induced necrosis of the skin. Ann Plast Surg. 1995;34(2):203-8.

24. Au AF, Fosnot J, Wu LC. Coumadin-induced skin necrosis of the breasts: case report. Ann Plast Surg. 2012;69(1):109-10.

25. Llamas-Velasco M, Alegría V, Santos-Briz Á, Cerroni L, Kutzner H, Requena L. Occlusive Nonvasculitic Vasculopathy. Am J Dermatopathol. 2017 Sep;39(9):637-62.

26. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:160S-98S.

27. Lewandowski K, Zawilska K. Protein C concentrate in the treatment of warfarin-induced skin necrosis in the protein C deficiency. Thromb Haemost. 1994;71:395.

28. Lane DA, Mannucci PM, Bauer KA, Bertina RM, Bochkov NP, Boulyjenkov V, et al. Inherited thrombophilia: Part 1. Thromb Haemost. 1996;76:651-62.

29. Karimi K, Odhav A, Kollipara R, Fike J, Stanford C, Hall JC. Acute Cutaneous Necrosis: A Guide to Early Diagnosis and Treatment. J Cutan Med Surg. 2017 Sep/Oct;21(5):425-37.

30. Bakoyiannis C, Karaolanis G, Patelis N, Maskanakis A, Tsaples G, Klonaris C, et al. Dabigatran in the Treatment of Warfarin-Induced Skin Necrosis: A New Hope. Case Rep Dermatol Med. 2016;2016:3121469.

ATYPICAL STERNAL PAIN IN A BREAST CANCER PATIENT MIMICKING ACUTE MYOCARDIAL INFARCTION

Dor esternal atípica no câncer de mama mimetizando infarto agudo do miocárdio

René Aloisio da Costa Vieira[1]*, Alessandra Coelho Santos[1], Idam de Oliveira-Junior[1],
Kátia Mathias Teixeira da Silva[1], Sérgio Luiz Brasileiro Lopes[1], Carlos Eduardo Paiva[1]

ABSTRACT

Radiation therapy on the left side of the chest, some chemotherapy drugs, and trastuzumab raise the risk of cardiac events. Acute chest pain associated with breast cancer is not common, but it is possible. Electrocardiogram, which can result normal in up to 80% of cases of infarction, and serial dosing of myocardial necrosis markers are fundamental for differential diagnosis. Total creatine kinase (CK), creatine kinase-MB fraction (CK-MB), and troponins are frequently used. We present the case of a patient with atypical chest pain associated with elevation of CK and CK-MB, whose evolution and complementary exams showed to be a thoracic tumor recurrence. We discuss the use of these markers for acute chest pain; possible differential diagnoses, the use of CK-MB relative index and, particularly, the presence of macro CK in some breast cancer patients — which in the case herein presented was a marker of tumor progression.

KEYWORDS: Breast neoplasms; recurrence; myocardial infarction; differential diagnosis; non-st elevated myocardial infarction.

RESUMO

A radioterapia do lado esquerdo do tórax, alguns quimioterápicos e o trastuzumabe elevam o risco de eventos cardíacos. A dor torácica aguda associada ao câncer de mama não é um evento frequente, mas é possível. No diagnóstico diferencial, faz-se necessário o eletrocardiograma, que pode ser normal em até 80% dos infartos, e a dosagem seriada de marcadores de necrose miocárdica, sendo frequentemente utilizados a creatinoquinase (CK) total, a creatinnoquinase fração MB (CK-MB) e as troponinas. Apresentamos o caso de uma paciente com dor torácica atípica associada à elevação sérica da CK e da CK-MB, sendo que a evolução e os exames complementares mostraram tratar-se de uma recorrência tumoral torácica. Discutem-se a utilização desses marcadores na dor torácica aguda, os diagnósticos diferenciais possíveis, a utilização do índice relativo CK-MB e, em especial, as macro CK presentes em algumas portadoras de câncer de mama, o que, nessa paciente, foi um marcador de progressão tumoral.

PALAVRAS-CHAVE: Neoplasias da mama; recidiva; infarto do miocárdio; diagnóstico diferencial; infarto do miocárdio sem supradesnível do segmento ST.

INTRODUCTION

Breast cancer treatment is a multidisciplinary effort based on association of radiotherapy, cytotoxic chemotherapy, hormone therapy, and target therapy. In addition to age, some types of cancer treatment may lead to increased risk of cardiovascular disease. Reports are contradictory regarding the relation between radiotherapy and risk of acute myocardial infarction (AMI).[1,2] A study carried out with patients submitted to lumpectomy and radiotherapy showed different risk ratios depending on the side irradiated. Patients with left-side breast cancer who have been submitted to radiotherapy presented with a significant 1% increase in AMI incidence.[3] On the other hand, tamoxifen[2] and raloxifene[4] were not related to increased risk of AMI. When it comes to chemotherapy and target therapies, doxorubicin is associated with cardiac complications in 4-36% of cases; paclitaxel causes bradycardia, bundle branch block or arrhythmia in 0.5% of patients; and trastuzumab causes cardiac events in 1.7-5.0% of patients. When the development of myocardial ischemia was assessed, 5-Fluorouracil was found to be associated with it in 1-68% of cases (more common in cases of continuous infusion), docetaxel in 1,7% of cases, and paclitaxel in 1-5% of cases.[5]

Acute chest pain is not a common event among patients with breast cancer, as there is a limited number of studies addressing this subject. Previous studies analyzed possible association of AMI occurrence with the use of doxorubicin[6] and tamoxifen,[7] and described cases of left bundle branch block during treatment with trastuzumab.[8]

Although electrocardiogram is mandatory when AMI is suspected, up to 80% of infarctions occur without any alteration shown in examinations. In these terms, markers of myocardial necrosis revolutionized AMI diagnosis. In Brazil, until recently, only creatine kinase (CK) and creatine kinase-MB (CK-MB) were recommended as markers. When available, troponin alone is currently recommended for being more specific to the myocardium. However, we are in a transitional phase since troponin is not available in all services.

Because of its frequency in the general population, AMI should always be considered in differential diagnosis of severe and short-term chest pain. In this paper, we describe the case of a patient with breast cancer presenting with severe chest pain of recent onset. Electrocardiogram showed absence of ST segment elevation. CK and CK-MB levels were elevated. Complementary tests and evolution of the picture showed a false positive result.

CASE REPORT

We report the case of a female diabetic patient, aged 47 years, with left-sided breast cancer, T3N1M0, stage IIIA, Luminal B, HER2/neu-positive. She was submitted to neoadjuvant chemotherapy – paclitaxel 80 mg/m^2/week for 12 weeks associated with trastuzumab in a loading dose of 8 mg/kg followed by 6 mg/kg every 21 days; 4 cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 21 days — with partial clinical response. After neoadjuvant chemotherapy, the patient underwent skin-sparing mastectomy associated with contra-lateral mastopexy and axillary lymphadenectomy levels I, II and III. Anatomopathological examination found pathological partial response (yT1micYpN0). She was submitted to 17 cycles of adjuvant trastuzumab supplementation (1-year treatment) followed by radiotherapy of chest wall (5000 cGy). She was in adjuvant hormone therapy taking anastrozole 1 mg/daily and goserelin for ovarian suppression. Thirty-two months after mastectomy, the patient returned with a complaint of precordial and retrosternal pain radiating to the back for one week and partial improvement with the use of anti-inflammatory drugs. She also reported asthenia and inappetence. Plain chest x-ray and electrocardiogram were normal (Figure 1A). Biochemical analysis showed glutamic oxaloacetic transaminase (GOT) 238 U/L, glutamic-pyruvic transaminase (GPT) 128 U/L, CK 1144 U/L, CK-MB 2340 IU/L and troponin <0.1 ng/mL. Follow-up examinations 6 and 12 hours later showed similar results. Therefore, the initial hypothesis of AMI was discarded.

Echocardiogram showed ejection fraction of 72% and absence of changes in segmental contractility. Computed tomography (CT)
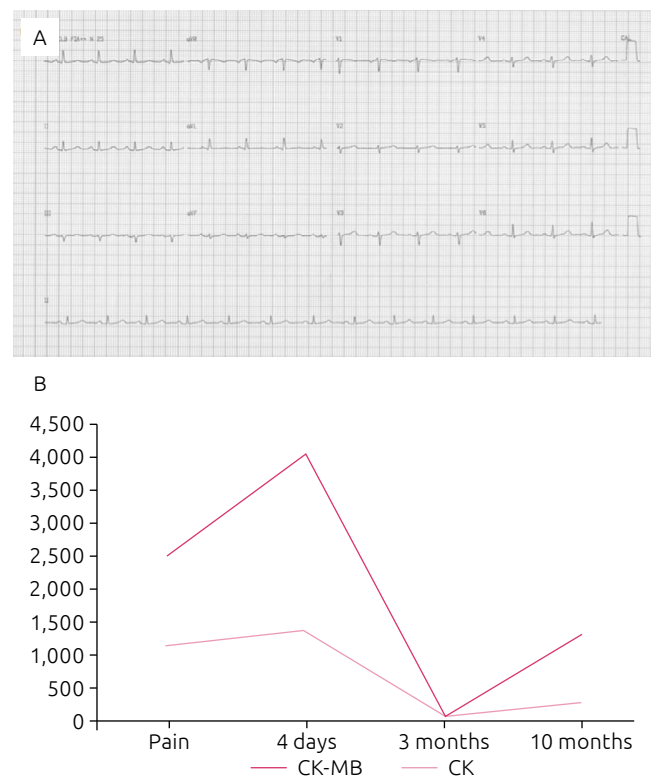

Figure 1. (A) ECG in clinical picture of pain; (A) Enzymatic curve for CK and CK-MB enzymes in response to treatment and recurrence.

scan of the chest and whole abdomen revealed a solid mass in left retrosternal and parasternal regions (8.5 x 4.6 cm) involving internal mammary artery, associated with a lytic osseous lesion in the sternal manubrium, suspicious pulmonary nodules and multiple liver metastases (Figure 2).

First-line palliative chemotherapy was started with weekly paclitaxel associated with trastuzumab. A 3-month follow-up CT examination showed disappearance of the mediastinal mass, pulmonary nodules and lytic sternal area, with decrease of the hepatic lesion (Figures 3A, 3B and 3C). Normalization of cardiac enzymes (Figure 1B) and liver transaminases were then seen. The patient completed 12 cycles of paclitaxel associated with trastuzumab. Post-treatment skeletal scintigraphy was normal. Chest CT showed reduction of the pulmonary disease and disappearance of the sternal lesion with stable liver disease. Due to
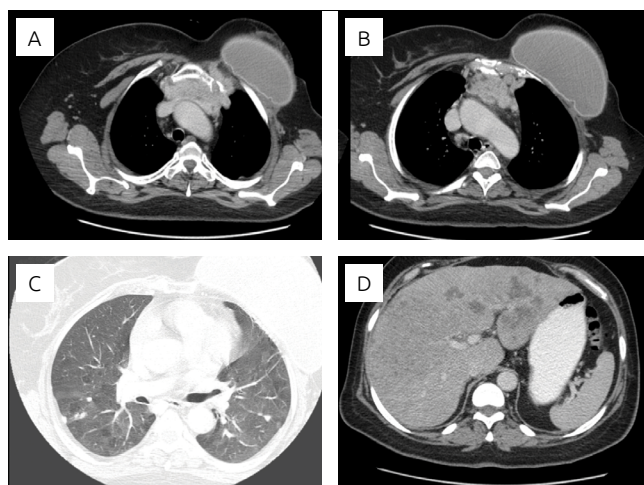

Figure 2. Tomography in clinical picture of pain: (A) thoracic mass with sternal invasion; (B) associated lymphadenomegaly; (C) lung metastasis; (D) liver metastasis.
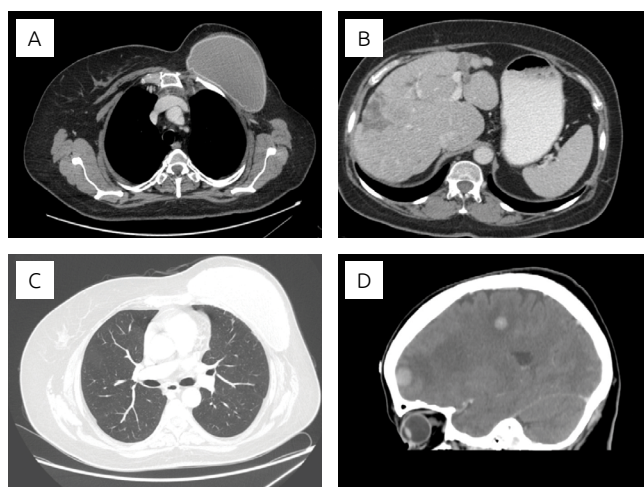

Figure 3. Response to chemotherapy: (A, B, and C) Tomography at three months showing regression; (D) Tomography at ten months showing brain recurrence.

clinical and radiological improvements, the patient was started on exemestane with trastuzumab maintenance therapy. Ten months after the beginning of palliative care, the patient sought medical attention with complaints of headache and dizziness. Cranial CT scan revealed bilateral multiple brain metastases (Figure 3D), CK 291 U/L and CK-MB 1,073 IU/L. The patient was submitted to palliative radiosurgery, with progression of disease and obit two months after the onset of brain recurrence (15 months after the first recurrence). The enzymatic curve is shown in Figure 1B.

DISCUSSION

Pain in the area under treatment is a frequent complaint among breast cancer patients. However, this discomfort is mild and often associated with local denervation and radiation therapy side effects. Other common symptoms include neuropathic pain, pain related to local recurrence, metastatic bone disease or lung/pleural disease, and degenerative changes of the shoulders. Although complementary exams have limited sensitivity/specificity in cases of severe recurrent pain, they are reliable for a correct etiological diagnosis. The literature reports a patient with suspected angina submitted to myocardial perfusion imaging with positron emission computed tomography (PET-CT), which revealed thoracic osseous recurrence.[9]

AMI is a potentially fatal entity, and differential diagnosis should be considered when facing severe and acute chest pain. Atypical chest pain, diabetes mellitus, and old age makes AMI diagnosis difficult. Normal electrocardiogram results are another worth mentioning element, since up to 80% of AMI cases lack the classical ST-segment elevation. Enzymes previously used in clinical practice, such as CK and CK-MB, are currently less used and replaced by more specific markers such as troponins. Nevertheless, the literature describes the case of a patient with chest pain, ST segment alteration, T-wave inversion and elevated troponin, but no changes in coronary arteries. In that specific case, chest pain was being caused by heart metastasis.[10]

Laboratory diagnosis of AMI has evolved a lot in recent decades. Initial markers include LDH (lactic dehydrogenase), AST, and CK. Advances in electrophoresis allowed identifying specific enzymes such as CK-MB.[11] CK-MB sensitivity depends on time, varying from 40-76% in the first four hours and to 60-100% in up to 12 hours, with 85-100% specificity.[12] Currently, the evaluation of serum troponin is associated with high sensitivity and specificity in cases of myocardial necrosis, the protein being able to detect small myocardial lesions.[13] Laboratory test is chosen when AMI is suspected. However, CK and CK-MB are still to be investigated whenever laboratory conditions for troponin analysis are poor.[13]

CK is a molecule found in large quantities in skeletal and cardiac muscles, also found in the brain and kidneys. CK enzymes consist of two types of subunits: the B type (predominant in the

brain) and M type (predominant in skeletal muscle). These enzymes are able to combine to create three isoenzymes — CK-BB, CK-MB, and CK-MM —, running with the approximate size of 80-kDa dimer during electrophoresis. Elevations of CK-MB are associated with trauma, muscular dystrophy, myositis, and vigorous exercise. False-positives can occur in conditions associated with elevated CK.[12] Two atypical types have higher molecular weights (greater than 200kDa) and are classified as macro CK. Macro CK types 1 and 2 are found in 0.43% and 1.2% of the population, respectively. Macro CK type 1 generally occurs in subjects with rhabdomyolysis, and may also be present in cancer patients. Macro CK type 2, in turn, usually occurs in patients with malignant neoplasias including prostate and breast cancers.[14,15] The order of migration of CK isoenzymes with electrophoresis is CK-BB, followed by CK-MB, then CK-MM. Macro CK type 1 can migrate to or between CK-MB and CK-MM regions; macro CK type 2 migrates after CK-MM fraction,[16] which may be a confounding factor for AMI diagnosis depending on the methodology used. Thus, CK-MB mass dosage may be overestimated in situations where the serum concentrations of macro CK-BB are excessive.[17]

Therefore, the serum level of macro-CK-BB should be measured to confirm a false-positive result. From then on, the use of other methods for CK-MB in AMI evaluation should be considered (such as the relative CK-MB index [IR CK-MB = 100 (CK-MB/CK total)], in which values between 5% and 25% are associated with heart-related changes, and values above 25% indicate possible interference by CK-BB or macro CK).[17]

In our case described, sternal metastasis was the reason of local pain. The titers of CK and CK-MB enzymes made us suspect of AMI, which was discarded by the relation between results and normal serial troponin values. Etiological diagnosis was only confirmed after tomography and by exclusion. Metastatic disease was then confirmed, with decrease in CK and CK-MB levels as a therapeutic response and elevation of these markers after further disease progression (Figure 1C). Thus, CK and CK-MB enzymes were to be considered tumor markers in the case we depicted, and this is not a common fact in clinical practice. The present report is justified by the discussion about the limitation of CK and CK-MB in AMI investigation, especially when there is association with breast cancer, in which macro CK-BB is proven present.

REFERENCES

1. Doyle JJ, Neugut AI, Jacobson JS, Wang J, McBride R, Grann A, et al. Radiation therapy, cardiac risk factors, and cardiac toxicity in early-stage breast cancer patients. Int J Radiat Oncol Biol Phys. 2007;68(1):82-93.

2. Geiger AM, Chen W, Bernstein L. Myocardial infarction risk and tamoxifen therapy for breast cancer. Brit J Cancer. 2005;92(9):1614-20.

3. Paszat LF, Mackillop WJ, Groome PA, Schulze K, Holowaty E. Mortality from myocardial infarction following postlumpectomy radiotherapy for breast cancer: a population-based study in Ontario, Canada. Int J Radiat Oncol Biol Phys. 1999;43(4):755-62.

4. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. New Eng J Med. 2006;355(2):125-37.

5. Schlitt A, Jordan K, Vordermark D, Schwamborn J, Langer T, Thomssen C. Cardiotoxicity and oncological treatments. Dtsch Arztebl Int. 2014;111(10):161-8.

6. Winchester DE, Bavry AA. Acute myocardial infarction during infusion of liposomal doxorubicin for recurrent breast cancer. Breast J. 2010;16(3):313-4.

7. Nakagawa T, Yasuno M, Tanahashi H, Ohnishi S, Nishino M, Yamada Y, et al. A case of acute myocardial infarction. Intracoronary thrombosis in two major coronary arteries due to hormone therapy. Angiology. 1994;45(5):333-8.

8. Tu CM, Chu KM, Yang SP, Cheng SM, Wang WB. Trastuzumab (Herceptin)-associated cardiomyopathy presented as new onset of complete left bundle-branch block mimicking acute coronary syndrome: a case report and literature review. Am J Emerg Med. 2009;27(7):903.e1-3.

9. Ceriani L, Giovanella L. Symptomatic sternal metastasis mimicking cardiac angina discovered by Tc-99m sestamibi myocardial perfusion scintigraphy. Tumori. 2008;94(3):437-9.

10. Auer J, Schmid J, Berent R, Niedermair M. Cardiac metastasis of malignant melanoma mimicking acute coronary syndrome. Eur Heart J. 2012;33(5):676.

11. Danese E, Montagnana M. An historical approach to the diagnostic biomarkers of acute coronary syndrome. Ann Transl Med. 2016;4(10):194.

12. Karras DJ, Kane DL. Serum markers in the emergency department diagnosis of acute myocardial infarction. Emerg Med Clin North Am. 2001;19(2):321-37.

13. Cardiologia SBd. V Diretriz da Sociedade Brasileira de Cardiologia sobre tratamento do infarto agudo do miocárdio com supradesnível do segmento ST. Arq Bras Cardiol. 2015;105(2 Suppl. 1):5-7.

14. Camarozano ACA, Henriques LMG. Uma macromolécula capaz de alterar o resultado da CK-MB e induzir ao erro no diagnóstico de infarto agudo do miocárdio. Arq Bras Cardiol. 1996;66(3):143-8.

15. Tsung JS. Creatine kinase and its isoenzymes in neoplastic disease. CRC. 1986;23(1):65-75.

16. Lee KN, Csako G, Bernhardt P, Elin RJ. Relevance of macro creatine kinase type 1 and type 2 isoenzymes to laboratory and clinical data. Clin Chem. 1994;40(7 Pt 1):1278-83.

17. Serdar MA, Tokgoz S, Metinyurt G, Tapan S, Erinc K, Hasimi A, et al. Effect of macro-creatine kinase and increased creatine kinase BB on the rapid diagnosis of patients with suspected acute myocardial infarction in the emergency department. Military Med. 2005;170(8):648-52.

INSTRUCTIONS TO AUTHORS

Introduction

Mastology is an international, multidisciplinary Journal, and official publication of the Brazilian Society of Mastology. It focuses on translational and clinical research of breast diseases. All manuscripts will be initially acessed by the Editor for suitability for the Journal. Papers deemed suitable are then evaluated by at least two independet expert reviewers, in a blind-review process to assess the scientific quality of the paper. The Editor is responsible by the final decision regarding acceptance of rejection of articles. Those that do not have merit, which contain significant methodological errors, or that do not fit into the editorial policy of the Journal will be rejected and can not be appealed. The reviewers' comments will be returned to the Authors for modifications in the text or justification of their conservation. Only after final approval of the reviewers and Editors, will the manuscripts be forwarded for publication. All manuscripts accepted for publication shall become the property of the Journal and may not be edited, in whole or in part, by any other means of dissemination, without the prior written authorization issued by the Editor-in-Chief.

Ethics

If the paper involves the use of human subjects, the Authors should ensure that it has been carried out in accordance with The Code of Ethics of the World Medical Association(Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed. All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The Journal will not accept editorial material for commercial purposes.

Submission of manuscripts

Articles can be sent in Portuguese, Spanish or English. After approved, all papers will be translated to English. *Mastology* publishes the following categories: Editorials, Original Articles, Short Communications, Review Articles, Images in Mastology, Case Reports, Technical Innovations, and Letters to the Editor.

Original Articles: Describes experimental research or clinical research – prospective or retrospective, randomized or double blind. They must have 3,000 to 5,000 words, excluding illustrations (tables, figures [maximum of 5]) and references [maximum of 30]. Manuscripts containing original clinical or experimental research results will be prioritized for publication. All manuscripts must present: Title in English, Structured Abstract, Keywords, Abstract, Keywords, Introduction, Methods, Results, Discussion, Conclusions and References.

Short Communications: Reports on important new results that fall within the scope of the journal may be submitted as short communications. These papers should not exceed 2,000 words in length and 20 references, and should follow the structure of an original research paper.

Review Articles: Systematic critical evaluation of the literature on a given subject, so as to contain a comparative analysis of the works in the area, which discusses the limits and methodological scope, allowing to indicate perspectives of continuity of studies in that line of research and should contain conclusions. The procedures adopted for the review, as well as the search, selection and evaluation strategies of the articles should be described, clarifying the delimitation and limits of the theme. Its maximum length should be 5,000 words and the maximum number of bibliographical references of 60.

The selection of themes is based on planning established by the Editor-in-Chief and Co-Editors. Articles in this category are usually ordered by publishers from authors with proven experience in the field. Spontaneous contributions may be accepted. It must present: Title, Abstract (without need of structuring), Keywords, Text (with or without subtitles), and References. The general instructions for figures, tables and references are the same as for the original articles.

Images in Mastology: Unusual images in clinical practice or associated with topics which are considered as rare. The text will be continuos, expressing the rarity or singularity of the case, at maximum of 400 words, and no more than 10 references and 3 figures. They must present: Title, Abstract (non-structurated up to 150 words), Keywords, and References.

Case reports: They are manuscripts reporting unpublished, highly interesting and well-documented clinical cases from a clinical and laboratorial point of view. The text should express the rarity or singularity of the case, at maximum of 2,000 words, and no more than 20 references and 3 figures. They should observe the structure: Introduction, Case report (with patient description, results of clinical exams, follow-up, diagnosis), Discussion (with similarity data in the literature), and Conclusion. They must present: Abstract (unstructured), Keywords, and up to 20 References.

Letters to the Editor: They aim to comment or discuss papers published in the journal or report original research in progress. They will be published at the discretion of the Editors, with the corresponding reply where applicable. They must not exceed 600 words and 5 references.

Editorials: Editorials are comissioned by the Editors, commenting on relevant works of the Journal itself, relevant researches or communications from Editors. Authors who wish to contribute an Editorial to the Journal should contact the Editorial Office (biblioteca@sbmastologia.com.br) prior to writing and submitting the Editorial.

Preparation of the Manuscript

A) Cover sheet

- Title of the article, in Portuguese and English, containing between 10 and 12 words, without articles and prepositions. The Title should be motivating and should give an idea of the objectives and content of work;
- full name of each author, without abbreviations;
- indication of the academic degree and institutional affiliation of each author, separately. If there is more than one institutional affiliation, indicate only the most relevant;
- indication of the Institution where the work was done;
- name, address, fax and e-mail of the corresponding author;
- sources of research assistance, if any;
- declaration of non-existence of conflicts of interest.

B) Second sheet

Abstract and Descriptors: Abstract, in Portuguese and English, with a maximum of 250 words. For The original articles, should be structured (Objective, Methods, Results, Conclusions), highlighting the most significant data of the work. For case reports, revisions or updates and a previous note, the summary should not be structured. Below the abstract, specify at least five and at most ten descriptors (Keywords) that define the subject of the work. The descriptors should be based on the DECS – Descriptors in Health Sciences – available at http://www.decs.bvs.br

C) Text

You should strictly obey the structure for each category of manuscript.

In all manuscript categories, the citation of the authors in the text should be numeric and sequential. Using Arabic numerals in parentheses and envelopes.

The standards to be followed were based on the format proposed by the International Committee of Medical Journal Editors and published in the article Uniform requirements for manuscripts submitted to biomedical journals also available for consultation at http://www.icmje.org/.

Presentation of the text

Preferably use the Microsoft Word® word processor.

Do not emphasize excerpts from the text: do not underline and do not use bold. Do not use capital letters in proper nouns (other than the first letter) in the text or Bibliographical References. When using acronyms or abbreviations, describe them in full the first time they are mentioned in the text.

Summary

The Summary should contain the relevant information, allowing the reader to get a general idea of the work. All articles submitted must have a summary in Portuguese or Spanish and in English (abstract), between 150 and 250 words. For Original Articles, abstracts should be structured including objectives, methods, results and conclusions. For the other categories, the format of the abstracts may be the narrative, but preferably with the same information. They should not contain quotations and abbreviations. Highlighting at least three and at most six indexing terms, extracted from the vocabulary "Descriptors in Health Sciences" (DeCS – www.bireme.br), when accompanying the abstracts in Portuguese or Spanish, and Medical Subject Heading – MeSH (Http://www.nlm.nih.gov/mesh/), when they follow the "Abstract". If no descriptors are available to cover the subject of the manuscript, terms or expressions of known use may be indicated.

Introduction

In this section, show the current state of knowledge about the topic under study, divergences and gaps that may possibly justify the development of the work, but without extensive review of the literature. For Case Reports, present a summary of the cases already published, epidemiology of the reported condition and a justification for the presentation as an isolated case. Clearly state the objectives of the work.

Methods

Start this section indicating the work planning: whether prospective or retrospective; Clinical or experimental trial; Whether the distribution of cases was random or not, and

so on. Describe the criteria for selection of patients or experimental group, including controls. Identify the equipment and reagents used. If the applied methodology has already been used, give the references in addition to the brief description of the method. Also describe the statistical methods employed and the comparisons for which each test was used. In the Case Reports, the sections Material and Methods and Results are replaced by the description of the case, remaining the remaining cases.

Results

It should be limited to describing the results found without including interpretations and comparisons. Present the results in logical sequence, with text, tables and figures.

Discussion

It should properly and objectively explore the results, discussed in light of other observations already recorded in the literature, highlighting the new and original information obtained in the research. Emphasize the appropriateness of the research methods used. Compare and relate the observations with those of other authors, commenting and explaining the differences that occur. Explain the implications of the findings, their limitations, and make recommendations. The discussion should culminate with the conclusions, indicating ways for new research or implications for professional practice. For Case Reports, base the Discussion on a broad and updated literature review.

Thanks

Collaborations of individuals, institutions or acknowledgments for financial support, technical aids, deserving recognition, but not justifying inclusion as the author, should be included.

References

References should be listed at the end of the article, numbered consecutively, following the order in which they were first mentioned in the text, based on the Vancouver style (see: "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Medical Publication "[http://www.nlm.nih.gov/bsd/uni-form_requirements.html]). All authors and works cited in the text should be included in this section and vice versa. Articles accepted for publication may be cited accompanied by the expression: accepted and awaiting publication, or "in press" indicating the periodical, volume and year.

For all references, cite all authors up to six. When in greater numbers, cite the first six authors followed by the expression et al. Examples:

Articles of Journals or Magazines

Del Giglio A, Pinhal MA. Genetic profile in breast cancer: a brief review for the mastologist. Rev Bras Mastologia. 2005; 15 (1): 45-50.

My Account

Montoro AF. Mastology. São Paulo: Sarvier, 1984.

Book Chapters

Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap III LC, Wenstrom KD. Williams Obstetrics. 22nd ed. New York: McGraw-Hill; 2005. Chapter 39, Multifetal gestation. P. 911-43.

With authorship

Von Hoff DD, Hanauske AR. Preclinical and early clinical development of new anticancer agents. In: Kufe DW, Bast RC Jr, Hait WN, Hong WK, Pollock RE, Weichselbaum RR, et al. Editors. Holland-Frei cancer medicine. 7th ed. Hamilton (ON): BC Decker Inc.; 2006. p. 600-16.

Theses and Dissertations

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

Electronic publications

Henrique MA, Cosiski MHR. Mammographic density as a risk factor for breast cancer. Rev Bras Ginecol Obstet [Internet]. 2007 [cited 2008 Feb 27]; 29 (10): 493-6.

Tables and Figures

The presentation of this material should be in black and white, on separate sheets, with captions and respective numbers printed next to each illustration. The name of the manuscript and authors must be noted on the back of each figure and table. All tables and figures should also be sent in digital files, preferably in Microsoft Word® files and the rest in Microsoft Excel®, Tiff or JPG files. The quantities, units and symbols used in the tables must comply with the national nomenclature. Surgery and biopsy photographs where colorations and special techniques were used will be considered for color printing and the authors will be responsible for the additional cost.

Captions: Print the captions using double space, accompanying the respective figures (graphics, photographs and illustrations) and tables. Each caption should be numbered in Arabic numerals, corresponding to its citations in the text.

Abbreviations and Acronyms: They must be preceded by the full name when first mentioned in the text. In tables, figures should be to contain their meaning below the table.

If the illustrations have already been published, they must be accompanied by written authorization from the author or publisher, with the reference source where it was published.

The text entered in the program "Word for Windows, with double space, with letters of size that makes reading easier (we recommend those of No. 14). It must be submitted electronically through the address: revistabrasileirademastologia@gmail.com

The Brazilian Journal of Mastology reserves the right not to accept for evaluation the articles that do not fulfill the criteria formulated above.

Submission of the manuscript

The manuscript must be accompanied by a letter signed by all the authors, authorizing its publication, stating that it is unpublished and that it was not, or is being submitted for publication in another periodical.

All persons designated as authors must respond for the authorship of the manuscript and have participated sufficiently in the work to assume public responsibility for its content. Authorship credit should be based only on substantial contributions during: (1) designing, planning, executing, analyzing and interpreting the results, (2) writing or reviewing the manuscript in an intellectually important way, and (3) Be published. Editors may request justification for inclusion of authors during the review process, especially if the total number of authors exceeds six.

They should be sent

- Declaration of Conflict of Interests, as relevant, The Declaration of Conflict of Interests, according to Resolution of the Federal Council of Medicine in 1595/2000, prohibits that in a scientific article is made promotion or advertisement of any commercial products or equipment.
- Certificate of Work Approval by the Research Ethics Committee Institution in which it was performed.
- Information on possible sources of research funding.
- Article dealing with clinical research with humans should include a statement that the Participants signed an Informed Consent Form.

The works must be submitted through the electronic address:
http://www.rbmastologia.com.br/

Título de Especialista em Mastologia

TEMa 2018 - Inscrições abertas até 22/05/2018

PROVAS:

Dias 10 e 11/07
Belém (PA)

Sócios quites da SBM ou da AMB tem desconto de **50% NA INSCRIÇÃO.**

O Edital está disponível na área do médico do site da SBM:
www.sbmastologia.com.br/medicos

Sociedade Brasileira de Mastologia

APOIO:

GRUPO OAM

CURSO DE
ONCOPLASTIA
E RECONSTRUÇÃO MAMÁRIA

EDUCAÇÃO CONTINUADA TEÓRICO PRÁTICA DA SBM

✓ Curso teórico e prático com realização de cirurgias

✓ Técnicas cirúrgicas inovadoras

✓ Professores renomados

Próximas turmas em

Jaú (SP) e Goiânia (GO)

Mais informações:(21) 2220-7711
secretaria@sbmastologia.com.br

Sociedade Brasileira de
Mastologia