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CONTENTS

EDITORIAL
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NIPPLE SPARING: STANDARD OF CARE?

Poupadora de mamilos: padrão de cuidado?

Megan E. Miller[1], Virgilio S. Sacchini[2]*

INTRODUCTION

Over the past several decades, advances in the treatment of breast cancer have led to less radial types of surgery for both the breast and the axilla. First, the concept of breast-conserving therapy was introduced, followed by the adoption of sentinel lymph node biopsy to largely replace axillary lymph node dissection. For patients who require mastectomy, techniques have evolved from radial and modified radical mastectomy (MRM) to procedures which facilitate reconstruction and improve cosmesis: skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM). While both approaches remove the glandular breast tissue, SSM preserves the majority of the skin flap, and NSM additionally preserves the nipple areolar complex (NAC). Preservation of the NAC has been associated with improved body image, satisfaction with nipple appearance and sensitivity, and higher psychosocial and sexual well-being in patients who undergo NSM compared with SSM[1,2]. Recent studies have confirmed the oncologic safety of NSM and its successful application for risk reduction in patients at high risk for breast cancer[3-5]. Complication rates in recent years are comparable to those for other types of post-mastectomy reconstruction, likely a result of improving surgeon experience and wider application of NSM technique[3,5]. Given the continuously increasing rates of bilateral mastectomy and high demand for breast reconstruction[6], we must ask whether NSM should now be considered standard of care.

ONCOLOGIC SAFETY

Initial concerns regarding the safety of NSM from an oncologic perspective stemmed from the perceived risk of recurrence at the NAC due to preserved ductal tissue, as well as risk of local recurrence owing to incomplete removal of glandular tissue secondary to limitations of the technique. Among single-institution studies of patients undergoing NSM, local recurrence rates range from 2–11.7%, with recurrence in the NAC of 1.3–3.7%[7]. A pooled analysis of 73 studies including 12,358 NSM procedures reported an overall locoregional recurrence rate of 2.38% at mean follow-up of 38 months (range 7.4–156 months)[4]. At longer average follow-up of 78 months for 788 NSM patients, Sakurai et al.[8] demonstrated a local recurrence rate of 8.2% and a nipple relapse rate of 3.7%, but no significant difference was found in overall or disease-free survival between patients who underwent NSM compared to conventional mastectomy at 21 years. Similarly, the study with the longest mean follow-up to date of 101 months (range 32–126 months) reported similar rates of recurrence for patients undergoing SSM (10.4%), NSM (11.7%), and MRM (11.5%), with no significant differences in rates of distant metastasis or breast cancer-specific mortality[9]. The current literature therefore supports the oncologic safety of NSM, and ongoing studies with longer follow-up will continue to inform recommendations for its use in patients with breast cancer.

RISK REDUCTION

Due to its aesthetic appeal and potential for bilateral application, NSM is a particularly attractive option for risk reduction in patients at high risk of breast cancer secondary to BRCA 1/2 mutations or strong family history. In the small number of studies which have retrospectively examined outcomes after bilateral NSM for risk reduction, subsequent breast cancer was diagnosed in 0–1.2% of patients[7]. Yao et al.[10] assessed incidental cancers, complications, and locoregional recurrences in 201 BRCA 1/2 mutation carriers who underwent either prophylactic or therapeutic NSM. At mean follow-up of 32.6 months (range 1–76 months), there were four total cancer events, only one of which was in a risk-reduction patient, and none involved the NAC. In a review of 728 NSMs performed at Memorial Sloan Kettering Cancer Center between 2000 and 2013, 459 (63%) were risk reducing, and 177 (24%) were in patients with a BRCA 1/2 mutation or a genetic variant of uncertain significance[5]. At median follow-up of 49 months, there were no cases of local recurrence, and only one case of regional recurrence which was in a patient who underwent therapeutic NSM. The vast majority of patients in both studies underwent immediate reconstruction with low complication rates and favorable short-term outcomes. While longer-term results are needed to

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confirm these findings, current evidence supports the use of NSM for risk reduction in BRCA 1/2 carriers and other patients at high risk for breast cancer.

PATIENT OUTCOMES

Factors which motivate NSM include improvement in aesthetic outcomes and patient satisfaction associated with preservation of the NAC. Studies demonstrate that patients who undergo NSM have better body image, overall satisfaction, and psychosocial well-being when compared with patients who undergo SSM with or without nipple reconstruction[1,2,9]. Results from survey-based analyses describe overall satisfaction with modern NSM in 68–77% of patients, with nipple appearance rated as good or excellent in 66–88%, but nipple sensation rated good or excellent in only 10–40%[7]. Interestingly, there was a significant decrease in surgeons' rating of aesthetic outcome after both SSM and NSM with increasing time interval from surgery, though patient ratings did not change significantly over the same period[9]. However, as others have pointed out, satisfaction scores vary considerably based on methodology and survey instrument, and may be adversely affected by post-operative complications.

Complications of NSM are similar to those of SSM when combined with immediate reconstruction and include infection, hematoma, flap necrosis, implant loss, and capsular contracture; necrosis and loss of the NAC are, however, unique to NSM. The recent meta-analysis by Headon et al.[4] reported an overall complication rate of 22.3% with an incidence of partial or total nipple necrosis of 5.9%. This is higher than the 1.8% rate of NAC loss found in the study by Yao et al., the latter of which is more reflective of recent data showing a low rate of nipple loss (0.9–1.9%) in contemporary series[7,10]. While NSM has been associated with a higher rate of flap necrosis, most series report resolution without need for operative debridement, and rates of expander or implant loss of less than 4%[5,11]. Importantly, complication rates have decreased over time to a mean of 11.5% in studies published after 2013, likely reflecting greater operative experience with NSM technique and careful application to appropriately selected patients[4].

PATIENT SELECTION AND OTHER CONSIDERATIONS

For the first time in 2016, the U.S. National Comprehensive Cancer Network (NCCN) suggested that performance of NSM could be considered in selected patients with breast cancer with the following characteristics: early-stage, biologically-favorable invasive cancer or ductal carcinoma in situ (DCIS) at least 2 cm from the nipple (i.e., Nottingham grade 1 or 2, node-negative, HER2 negative, no lymphovascular invasion), with no evidence of malignancy at nipple margin assessment[12]. Absolute contraindications to NSM include pathologic nipple discharge, skin or nipple involvement such as Paget's disease or inflammatory carcinoma, and imaging findings suggesting malignant involvement of the nipple and subareolar tissues.

Studies assessing post-operative complications have identified additional factors which are variably adopted as relative contraindications to NSM. Smoking, prior radiation to the chest wall, and previous breast surgery affect tissue viability and may impair wound healing. Very large and/or ptotic breasts may increase the risk of flap and nipple necrosis and create a reconstructive challenge due to excess skin in the preserved envelope[13]. Patients who are obese or have multiple medical co-morbidities are not ideal candidates for NSM due to the increased risk of complications with complex surgery, reconstruction, and the associated longer operative time. However, in recent years, NSM has been used more widely in groups previously excluded from consideration, for example, in selected patients following neoadjuvant chemotherapy, and in those with prior breast incisions or macromastia[3,7].

One critical caveat to the ongoing discussion regarding oncologic, surgical, and patient-centered outcomes after NSM is the relative lack of long-term data. While the current evidence supports its use in well-selected patients, more robust follow-up is needed to determine its safety and efficacy in the wider population of women who may desire NSM.

CONCLUSIONS

Compared with SSM and MRM, NSM provides the advantage of preserving the NAC and maintaining its unique native color, size, and projection, characteristics which are difficult to reproduce with reconstructed nipples[13]. Loss of the NAC is considered by some to be as or even more psychologically significant than loss of the breast mound, which is readily replaced by either implant-based or autologous reconstruction. Given the greater overall satisfaction and psychosocial well-being reported in patients undergoing NSM compared with SSM, NSM should undoubtedly be considered when a patient requires or chooses mastectomy.

When evaluating whether a new procedure or treatment should be adopted as standard of care, it must be assessed for safety and efficacy. In addition, it must be not only non-inferior to the current standards, but also possess an element that is superior in some way—by decreasing morbidity or mortality, or by improving quality of care. NSM meets the latter criteria in providing superior patient-centered outcomes, favorable aesthetic results, and a gain in quality of life compared with the other types of mastectomy[14]. Both meta-analyses and single-institution studies have confirmed the oncologic safety of NSM in selected patients, and the NCCN supports its use in patients with early-stage, biologically favorable, peripheral breast cancer with negative nipple margins at histopathological assessment[4,5,11]. NSM is also efficacious for risk reduction in patients with BRCA

1/2 mutations and those at high risk of breast cancer, with low rates of recurrence and complications[7,10]. The major complication unique to NSM is necrosis of the NAC, the rate of which has decreased in recent years. Though undesirable, NAC loss essentially converts an NSM to an SSM, which does not compromise the therapeutic or prophylactic outcome from an oncologic standpoint. NSM is safe and efficacious, non-inferior to existing mastectomy techniques, and provides an added benefit to patients in psychosocial domains, thereby meeting the stipulations for a new standard of care.

However, it must be noted that NSM is not indicated for all patients, just as other "standards" such as sentinel lymph node biopsy are applied only in the appropriate clinical setting. NSM requires negative nipple margin assessment and must not be pursued in patients with carcinoma known or suspected to invade the NAC or subareolar tissue by clinical exam, presence of nipple discharge, or imaging findings. NSM should be carefully considered in patients with multiple co-morbidities, current smokers, and those who have had prior breast surgery or radiation. Close coordination with reconstructive surgery must be sought in such cases to minimize complications by planning appropriate incisions and perhaps performing staged procedures.

Given the rising incidence of both therapeutic and prophylactic bilateral mastectomies and the likelihood of identifying greater numbers of patients at high risk of breast cancer due to genetic testing, the demand for NSM is likely to increase. We must ensure that breast and reconstructive surgeons fully understand the indications and contraindications to this technique, and appropriately counsel patients regarding both oncologic and aesthetic outcomes. This should include discussing the limitations of short-term follow-up in the majority of studies, as well as potential operative complications, and the risks and benefits of NSM compared with SSM. However, with careful patient selection, shared decision making, and coordination of care, NSM can be confidently adopted in a subset of patients as standard of care for the treatment of breast cancer and for the reduction of breast cancer risk.

REFERENCES

1. Didier F, Radice D, Gandini S, Bedolis R, Rotmensz N, Maldifassi A, et al. Does nipple preservation in mastectomy improve satisfaction with cosmetic results, psychological adjustment, body image and sexuality? Breast Cancer Res Treat. 2009;118(3):623-33. https://doi.org/10.1007/s10549-008-0238-4
2. Wei CH, Scott AM, Price AN, Miller HC, Klassen AF, Jhanwar SM, et al. Psychosocial and sexual well-being following nipple-sparing mastectomy and reconstruction. Breast J. 2016;22(1):10-7. https://doi.org/10.1111/tbj.12542
3. Galimberti V, Vicini E, Corso G, Morigi C, Fontana S, Sacchini V, et al. Nipple-sparing and skin-sparing mastectomy: Review of aims, oncological safety and contraindications. Breast. 2017; 34(Suppl 1):S82-S84. https://doi.org/10.1016/j.breast.2017.06.034
4. Headon HL, Kasem A, Mokbel K. The oncological safety of nipple-sparing mastectomy: A systematic review of the literature with a pooled analysis of 12,358 procedures. Arch Plast Surg. 2016;43(4):328-38. https://doi.org/10.5999/aps.2016.43.4.328
5. Manning AT, Sacchini VS. Conservative mastectomies for breast cancer and risk-reducing surgery: the Memorial Sloan Kettering Cancer Center experience. Gland Surg. 2016;5(1):55-62. https://doi.org/10.3978/j.issn.2227-684X.2015.10.02
6. Jagsi R, Jiang J, Momoh AO, Alderman A, Giordano SH, Buchholz TA, et al. Trends and variation in use of breast reconstruction in patients with breast cancer undergoing mastectomy in the United States. J Clin Oncol. 2014;32(9):919-26. https://doi.org/10.1200/JCO.2013.52.2284
7. Hieken TJ, Boolbol SK, Dietz JR. Nipple-sparing mastectomy: indications, contraindications, risks, benefits, and techniques. Ann Surg Oncol. 2016;23(10):3138-44. https://doi.org/10.1245/s10434-016-5370-5
8. Sakurai T, Zhang N, Suzuma T, Umemura T, Yoshimura G, Sakurai T, et al. Long-term follow-up of nipple-sparing mastectomy without radiotherapy: a single center study at a Japanese institution. Med Oncol. 2013;30(1):481. https://doi.org/10.1007/s12032-013-0481-3
9. Gerber B, Krause A, Dieterich M, Kundt G, Reimer T. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. Ann Surg. 2009;249(3):461-8. https://doi.org/10.1097/SLA.0b013e31819a044f
10. Yao K, Liederbach E, Tang R, Lei L, Czechura T, Sisco M, et al. Nipple-sparing mastectomy in BRCA1/2 mutation carriers: an interim analysis and review of the literature. Ann Surg Oncol. 2015;22(2):370-6. https://doi.org/10.1245/s10434-014-3883-3
11. Piper M, Peled AW, Foster RD, Moore DH, Esserman LJ. Total skin-sparing mastectomy: a systematic review of oncologic outcomes and postoperative complications. Ann Plast Surg. 2013;70(4):435-7. https://doi.org/10.1097/SAP.0b013e31827e5333
12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology by Site: Breast Cancer [Internet]. [cited on July 26, 2017]. Available at: www.nccn.org
13. Spear SL, Hannan CM, Willey SC, Cocilovo C. Nipple-sparing mastectomy. Plast Reconstr Surg. 2009;123(6):1665-73. https://doi.org/10.1097/PRS.0b013e3181a64d94
14. Mota BS, Riera R, Ricci MD, Barrett J, de Castria TB, Atallah AN, et al. Nipple- and areola-sparing mastectomy for the treatment of breast cancer. Cochrane Database Syst Rev. 2016;11:Cd008932. https://doi.org/10.1002/14651858.CD008932.pub3

EDITORIAL
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THE REALITY OF PROPHYLACTIC NIPPLE-SPARING MASTECTOMY IN BRAZIL

Realidade da adenomastectomia redutora de risco no Brasil

Antonio Luiz Frasson[1]*, Martina Lichtenfels[2], Alessandra Borba Anton de Souza[2]

Surgical treatment of breast cancer has evolved over the past decades, from radical mastectomy to the acceptance of conservative techniques. In recent years, several studies have demonstrated the oncological safety and good aesthetic result of the skin-sparing mastectomy. Skin-sparing mastectomy consists in removal of the entire glandular breast tissue and the nipple-areola complex (NAC), preserving the skin of the breast[1-4]. Consequently, it favors immediate breast reconstruction using autologous tissue, expanders or silicone prosthesis. Based on this technique, researchers started to question the oncological safety and therapeutic indications to also preserve the NAC.

Nipple-sparing mastectomy involves surgical excision of the whole mammary gland, preserving the subcutaneous fat, the skin, and the NAC. As the breast envelope remains intact, it is extremely important to preserve the subcutaneous blood vasculature for the survival of skin and especially of NAC. In 1951, Rice and Stickler described this surgical technique for the first time for the treatment of a benign breast disease[5]. Currently, NSM has been performed for the treatment of patients in high-risk to develop breast cancer as a prophylactic surgery and in patients with malignant neoplasms[6].

Prophylactic nipple-sparing mastectomy has been proven a safe and effective technique for women with high risk of developing breast cancer[7-9]. Prophylactic surgeries become more widespread in society every day, with an increase in demand in recent years due to the development of models that calculate estimated risk of neoplasms, the increase in access to genetic tests to identify mutations associated with breast neoplasm, and the improvement of techniques and materials for surgical reconstruction.

Positive oncological family history can be very common in women diagnosed with breast or ovarian cancer, but heritable mutations are related to less than 10% of neoplasms of all patients with breast cancer, and less than 15% among patients with ovarian cancer. Mutations in BRCA1 and BRCA2 genes cause approximately 40 to 50% of hereditary syndromes related to breast and ovarian cancer, while mutations in genes such as TP53, PTEN, PALB2, CHEK2, STK11 are responsible for only 10%[10.11]. Remaining causes correspond to unknown genetic variants and mutations in other genes that are already known, but extremely rare[10,12.13]. Women with mutations in BRCA1 and BRCA2 genes presents an increased chance to develop breast and ovarian cancers. Throughout their whole life, the risk of developing breast cancer is about 55 to 85% and for ovarian cancer this number is around 15 to 65%[14,15]. These genes are also correlated with more aggressive tumors, increased risk for second cancer diagnosis, and the development of triple-negative breast tumors[16.17]. Salpingo-oophorectomy reduces the risk in patients with proven mutation for hereditary syndromes related to breast and ovarian cancers, and it was indicated as prophylactic surgery in the National Comprehensive Cancer Network (NCCN) Guideline. Since mastectomy only reduces the risk of breast neoplasm, the NCCN Guideline suggests a case-by-case discussion rather than formally indicating it as a prophylactic approach for the mentioned patients[18].

In Brazil, this technique has also been increasingly used, but data about it are scarce, as the literature lacks publications on the practice in Brazilian centers. To increase knowledge about prophylactic nipple-sparing mastectomy in Brazil and the opinion of mastologists on the subject, we conducted a survey using a questionnaire sent by *e-mail* to the members of the Brazilian Society of Mastology (BSM).

In all, 183 mastologists answered our questionnaire on prophylactic nipple-sparing mastectomy in Brazilian clinical practice. Out of these 183 participants, more than 50% were from the Southeast region, 18.6% from the South region, 17.5% from the Northeast region, and 11% from the Midwest and North regions. Most participants — approximately 70% — work in cities with more than 500 thousand inhabitants, that is, the large cities of Brazil where reference hospitals are located. Only 6% of them work in cities with less than 100 thousand inhabitants. Career lengths of mastologists who answered the questionnaire were:

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19% with 1 to 5 years, 21% with 5 to 10 years, 15% with 10 to 15 years, 17% with 15 to 20 years, and 29% with more than 20 years of experience. This information is interesting because it shows that both new and experienced mastologists took the survey, thus making it more heterogeneous. Most participants work in private (45.9%) and private/academic hospitals (39.9%), and 14.2% work in public hospitals.

A substantial number of mastologists who answered our questionnaire perform less than 5 nipple-sparing mastectomies per year (34.6%); approximately 25% perform 5 to 10 surgeries per year; 22%, 11 to 20 surgeries per year; and 19%, over 20 surgeries per year. The vast majority of nipple-sparing mastectomies were performed in patients with breast neoplasms (70% of patients had undergone less than 10% of prophylactic surgeries), and only 13.2% of mastologists had performed more than 50% of prophylactic surgeries out of the total number of nipple-sparing mastectomies.

The interest in prophylactic breast surgery had a significant increase by the Angelina Jolie effect, in 2013[19]. Patients all around the world sought doctors to get information on genetic testing and possible practices to prevent breast cancer development. Our data show that prophylactic surgeries still account for the minority of indications for nipple-sparing mastectomy in Brazil, but also that this number is increasing.

Another important characteristic is the small number of bilateral therapeutic surgeries when the patient does not have a neoplasm in the contralateral breast. Approximately 75% of mastologists perform bilateral surgery in only 20% of cases of therapeutic nipple-sparing mastectomies. A minority of surgeons (13%) perform bilateral surgeries with prophylactic surgery in contralateral breast in most of nipple-sparing mastectomies they conduct.

In the United States, the use of prophylactic nipple-sparing mastectomy in the contralateral breast has increased significantly in recent decades, despite bringing little benefit for patients with low risk of developing cancer in contralateral breast[20,21]. This phenomenon could be possibly related to greater access to high-quality screening tests, the availability of better techniques in breast reconstruction, as well as the choice of patients to undergo prophylactic surgery, motivated mainly by the fear of disease recurrence and by esthetic reasons (symmetry)[22,23].

In our study, we found that most mastologists do not perform bilateral nipple-sparing mastectomy, contrary to the trend in developed countries. The prophylactic surgery in contralateral breast prolongs patients' hospital stay, increases surgery costs, can lead to postoperative complications, and, so far, it has not demonstrated higher overall survival rate in patients with sporadic breast cancer who underwent this procedure[24,25]. We believe that these are the reasons why mastologists do not perform bilateral surgery in most patients in Brazil. However, not performing the surgery may influence the recurrence of breast neoplasm and also have unsatisfactory esthetic results, leading the patient to new surgical procedures and higher treatment costs. Therefore, discussing this topic is of great importance to find the best treatment for patients.

According to our questionnaire, paying patients and patients holding a health insurance have more access to genetic evaluation compared to those who rely on the Brazilian public health system (SUS). While 17% of the participants answered that all of their paying and/or insured patients have access to genetic evaluation, only 1% reported the same for their patients at SUS. Another striking fact is the poor access to genetic evaluation for the vast majority of SUS patients (85.6%). As most mastologists who took our survey are from major cities, we expected a greater number of SUS patients with access to geneticists.

When asked about the most common reason to indicate prophylactic bilateral nipple-sparing mastectomy, 64.8% of the participants declared that they only suggest prophylactic surgery for patients with BRCA1 and/or BRCA2 mutations. Only 7.7% stated recommending prophylactic surgery if the patient has a negative genetic test result for mutations in these genes, but positive family history of breast and/or ovarian cancer, and 11.5% usually indicate the technique for patients who did not undergo genetic testing, but have a family history of breast and/or ovarian cancer. A positive genetic test result for other genetic high-penetrance mutations lead only 1.1% of the participants to indicate prophylactic nipple-sparing mastectomy, and 9.3% of surgeons suggest prophylactic surgery when they find bilateral precursor lesions. These data demonstrate how the access to genetic testing is important before conducting this kind of procedure, and as many patients assisted at SUS institutions do not have such access, indication of prophylactic nipple-sparing mastectomy is limited.

In the questionnaire, the following hypothetical case was described: 45-year-old female patient, last menstrual period 15 days earlier, nulliparous, menarche at age 10, multiple bilateral breast nodules (category 3 in last breast imaging test), great-aunt with breast cancer at age 50, previous breast biopsy resulting in fibroadenoma, with 48% of risk throughout her life according to the International Breast Intervention Study (IBIS) Breast Cancer Risk Evaluation Tool. Negative test for mutations for *breast cancer gene* (BRCA — sequencing and *multiplex ligation-dependent probe amplification* — MLPA). In accordance with previous findings, most mastologists would not indicate prophylactic nipple-sparing mastectomy in this case (76%). As the patient presented no BRCA mutation, neither strong family history, which were the most common causes of recommendation of this type of surgery reported by participants, most mastologists did not consider it necessary.

This survey has contributed to increase the knowledge about indications, use and limitations of nipple-sparing mastectomy. However, these informations should be more deeply discussed in further studies.

REFERENCES

1. Medina-Franco H, Vasconez LO, Fix RJ, Heslin MJ, Beenken SW, Bland KI, et al. Factors associated with local recurrence after skin-sparing mastectomy and immediate breast reconstruction for invasive breast cancer. Ann Surg. 2002;235:814-9.
2. Carlson GW, Styblo TM, Lyles RH, Jones G, Murray DR, Staley CA, et al. The use of skin-sparing mastectomy in the treatment of breast cancer: The Emory experience. Surg Oncol. 2003;12:265-9.
3. Uriburu JL, Vuoto HD, Cogorno L, Isetta JA, Candas G, Imach GC, et al. Local recurrence of breast cancer after skin-sparing mastectomy following core needle biopsy: case reports and review of the literature. Breast J. 2006;12:194-8. https://doi.org/10.1111/j.1075-122X.2006.00240.x
4. Warren PA, Foster RD, Stover AC, Itakura K, Ewing CA, Alvarado M, et al. Outcomes after total skin-sparing mastectomy and immediate reconstruction in 657 breasts. Ann Surg Oncol. 2012;19(11):3402-9. https://doi.org/10.1245/s10434-012-2362-y
5. Rice CO, Strickler JH. Adeno-mammectomy for benign breast lesions. Surg Gynecol Obstet. 1951;93:759-62.
6. Benediktsson KP, Perbeck L. Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants: a prospective trial with 13 years median follow-up in 216 patients. Eur J Surg Oncol. 2008;34(2):143-8. https://doi.org/10.1016/j.ejso.2007.06.010
7. Hartmann LC, Schaid DJ, Woods JE, Crotty TP, Myers JL, Arnold PG, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med. 1999;340:77-84. https://doi.org/10.1056/NEJM199901143400201
8. De Felice F, Marchetti C, Musella A, Palaia I, Perniola G, Musio D, et al. Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis. Ann Surg Oncol. 2015;22:2876-80. https://doi.org/10.1245/s10434-015-4532-1
9. Ludwig KK, Neuner J, Butler A, Geurts JL, Kong AL. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. Am J Surg. 2016;212:660-9. https://doi.org/10.1016/j.amjsurg.2016.06.010
10. Castera L. Krieger S, Rousselin A, Legros A, Baumann JJ, Bruet O, et al. Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. Eur J Human Genet. 2014;22:1305-13. https://doi.org/10.1038/ejhg.2014.16
11. Silva FC, Lisboa BC, Figueiredo MC, Torrezan GT, Santos EM, Krepischi AC, et al. Hereditary breast and ovarian cancer: assessment of point mutation and copy number variations in Brazilian patients. BMC Med Genet. 2014;15:15:55. https://doi.org/10.1186/1471-2350-15-55
12. Campeau PM, Foulkes WD, Tischkowitz MD. Hereditary breast cancer: new genetic developments, new therapeutic avenues. Hum Genet. 2008;124:31-42. https://doi.org/10.1007/s00439-008-0529-1
13. Lhota F, Zemankova P, Kleiblova P, Soukupova J, Vocka M, Stranecky V, et al. Hereditary truncating mutations of DNA repair and other genes in BRCA1/BRCA2/PALB2 negatively tested breast cancer patients. Clin Genet. 2016;90(4):324-33. https://doi.org/10.1111/cge.12748
14. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994;266:66-71.
15. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;378:789-92. https://doi.org/10.1038/378789a0
16. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304(9):967-75. https://doi.org/10.1001/jama.2010.1237
17. Couch FJ, Hart SN, Sharma P, Toland AE, Wang X, Miron P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015;33:304-11. https://doi.org/10.1200/JCO.2014.57.1414
18. National Comprehensive Cancer Network. NCCN Clinical practice guidelines in Oncology [Internet]. Disponível em: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
19. Evans DGR, Barwell J, Eccles DM, Collins A, Izatt L, Jacobs C, et al. The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services. Breast Cancer Res. 2014;16(5):442. https://doi.org/10.1186/s13058-014-0442-6
20. Yao K, Stewart AK, Winchester DJ, Winchester DP. Trends in contralateral prophylatic mastectomy for unilateral cancer: a report from the National Cancer Data Base, 1998-2007. Ann Surg Oncol. 2010;17:2554-62. https://doi.org/10.1245/s10434-010-1091-3
21. Tuttle T, Jarosek S, Habermann E, Arrington A, Abraham A, Morris TJ, et al. Increasing rates of contralateral prophylatic mastectomy among patients with ductal carcinoma in situ. J Clin Oncol. 2009;27(9):1362-7. https://doi.org/10.1200/JCO.2008.20.1681
22. Ager B, Butow P, Jansen J, Phillips KA, Porter D; CPM DA Advisory Group. Contralateral prophylatic mastectomy (CPM): A systematic review of patient reported factors and psychological predictors influencing choice and satisfaction. The Breast. 2016;28:107-120. https://doi.org/10.1016/j.breast.2016.04.005
23. Brewster AM, Parker PA. Current knowledge on contralateral prophylatic mastectomy among women with sporadic breast cancer. Oncologist. 2011;16:935-41. https://doi.org/10.1634/theoncologist.2011-0022
24. Mortenson MM, Schneider PD, Khatri VP, Stevenson TR, Whetzel TP, Sommerhaug EJ, et al. Immediate breast reconstruction after mastectomy increases wound complications: however, initiation of adjuvante chemotherapy is not delayed. Arch Surg. 2004;139:988-91. https://doi.org/10.1001/archsurg.139.9.988
25. Murphy JA, Milner TD, O'Donoghue JM. Contralateral risk-reducing mastectomy in sporadic breast cancer. Lancet Oncol. 2013;14:e262-9. https://doi.org/10.1016/S1470-2045(13)70047-0

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CLINICAL AND HISTOPATHOLOGICAL AXILLARY ASSESSMENT

Avaliação clínica e histopatológica axilar após esvaziamento por câncer de mama

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ABSTRACT

Introduction: The proper selection of patients for sentinel lymph node biopsy is essential and depends on the evaluation of the patient's prediction for lymph node involvement and an evaluation of the accuracy of the clinical examination. **Objective:** This study aimed to evaluate the axillary contents of 102 breast cancer patients with tumors between 3 and 5 centimeters who underwent axillary dissection between January 2010 and December 2013. **Methods:** The data were categorized according to positive or negative axillary clinical evaluation and positive or negative anatomopathological evaluation. **Results:** The value for positive predictive values for physical examination was 83.5% and the negative predictive value was 34.88%. In addition, axillary physical examination showed 63.6% sensitivity and 60% specificity. Most patients with axillary involvement in the anatomopathological evaluation correlated with tumor grade, size, location and angiolymphatic invasion. **Conclusion:** It is believed that a better evaluation of the prediction of lymph node involvement, considering some clinicopathological risk factors in patients with suspicious lymph nodes, should be performed to aid the preoperative study of the axilla and the axillary approach screening.

KEYWORDS: Breast cancer; sentinel lymph node; diagnostic techniques, surgical.

RESUMO

Introdução: Atualmente, precisamos selecionar adequadamente as pacientes a serem submetidas à biópsia de linfonodo sentinela. Para isso, são imprescindíveis a avaliação da predição daquele paciente acerca do comprometimento linfonodal e a avaliação da acurácia do exame clínico. **Objetivo:** O presente estudo teve como objetivo avaliar o conteúdo axilar de pacientes portadoras de câncer de mama com tumores entre três e cinco centímetros submetidas ao esvaziamento axilar entre 2010 e 2013, por meio da análise de 102 prontuários. **Métodos:** Os dados foram categorizados segundo a avaliação clínica axilar positiva ou negativa e a avaliação anatomopatológica positiva ou negativa. **Resultados:** Observaram-se valor preditivo positivo do exame físico de 83,5% e preditivo negativo de 34,88%. O exame físico axilar mostrou sensibilidade de 63,6% e especificidade de 60%. A maioria das pacientes com comprometimento axilar no anatomopatológico mostrou correlação com o grau tumoral, tamanho, localização e invasão angiolinfática. **Conclusão:** Acredita-se que uma melhor avaliação quanto à predição do comprometimento linfonodal, levando em consideração alguns fatores clinicopatológicos de risco nas pacientes com linfonodos suspeitos, deve ser feita como auxílio no estudo pré-operatório da axila e triagem no tocante à abordagem axilar.

PALAVRAS-CHAVE: Neoplasias da mama; linfonodo sentinela, técnicas de diagnóstico por cirurgia.

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INTRODUCTION

Lymph node surgery in the treatment of breast cancer is focused on sentinel lymph node biopsy (SLNB)[1,2]. Currently, one of the principal contraindications for SLNB is the presence of clinically suspicious axillary lymph nodes. Despite this, physical examination is not a sensitive or reliable method to determine axillary status, since metastatic lymph nodes are often not palpable and reactive lymph nodes can be confused with metastatic nodes[3]. Thus, clinical examination of the axilla is highly susceptible to false-positive results and insufficiencies and cannot justify axillary lymphadenectomy[4].

The objective of this study was to evaluate lymph node involvement and the accuracy of the clinical examination of patients with tumors between 3 and 5 centimeters in order to compare the axillary approach.

MATERIALS AND METHODS

A retrospective study was carried out by analyzing the medical records of 102 breast cancer patients with invasive carcinoma of no special type (NST), with tumors between 3 and 5 centimeters, who underwent axillary lymph node dissection in the Mastology Service of the Liga Norte-Riograndense Contra o Câncer (LNRCC), in Natal, Rio Grande do Norte, Brazil, from 2010 to 2013. Patients receiving neoadjuvant chemotherapy were excluded. According to the LNRCC protocol at this time, all patients with tumors greater than 3 centimeters were automatically submitted to axillary lymph node dissection. Axillary dissection analysis was performed by standard techniques on hematoxylin/eosin stained from each lymph node sampled.

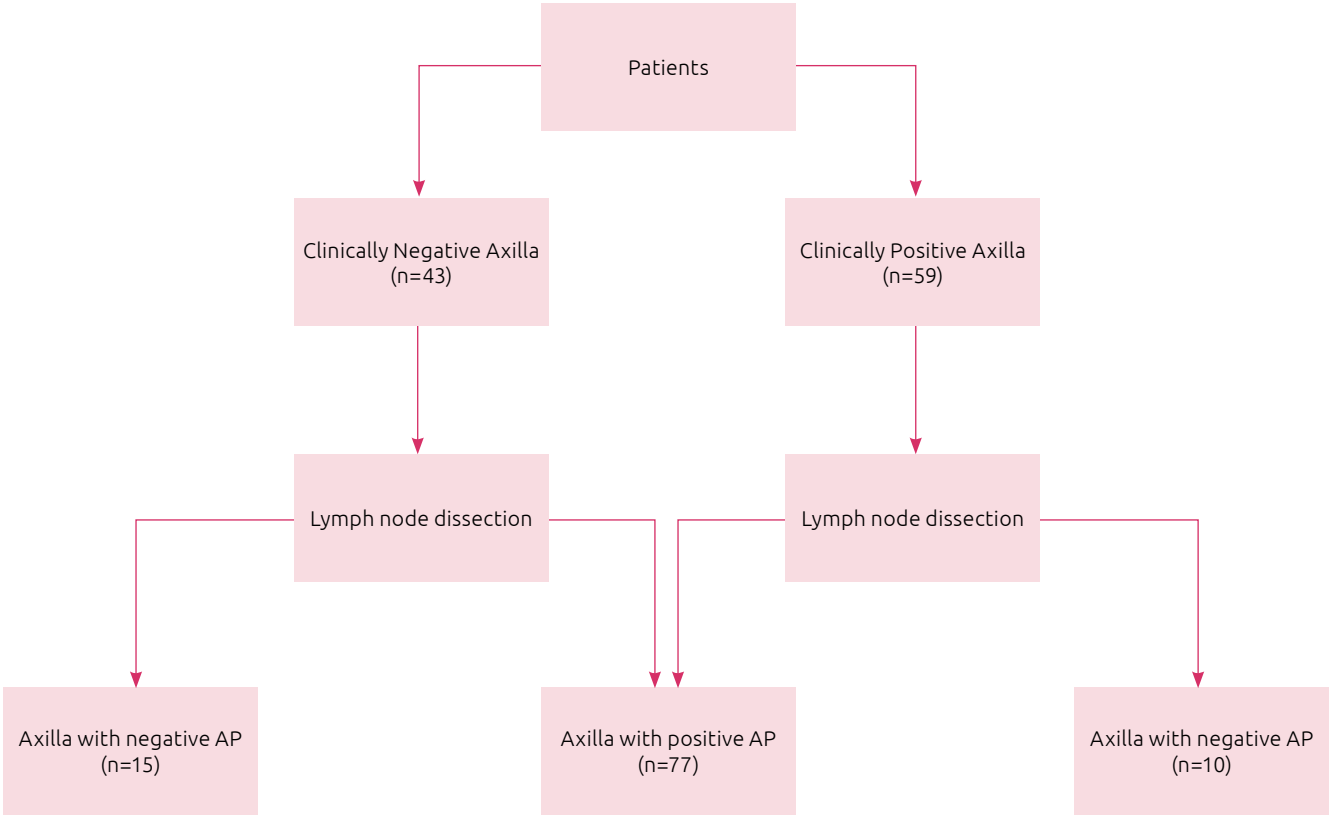
RESULTS

It was observed that 57.84% of the 102 patients were classified with positive axillary clinical staging, and, after the anatomopathological evaluation (AP), 75.49% of them presented a positive pathological axillary exam (Table 1). Thus, 83.05% of the patients with a clinically positive axilla had axillary involvement confirmed in the AP, with *odds ratio* (OR) = 23.84; 95% confidence interval (95% CI) 11.39–49.87, and p <0.0001. However, 65.12% of the patients who were

Table 1. Anatomoclinical correlation of axillary evaluation.

Physical exam	Positive axilla AP n (%)	Negative axilla AP n (%)	Total n (%)	OR (95%CI)	p
Positive (n=59)	49 (83.05)*	10 (16.95)	59 (100)	23.84 (11.39–49.87)	<0.0001
Negative (n=43)	28 (65.12)*	15 (34.88)	43 (100)	3.44 (1.92–6.16)	<0.0001

AP: anatomopathological evaluation; OR: *odds ratio*; 95%CI: 95% confidence interval; *statistically significant (p <0.0001) using Fisher's exact test.



AP: anatomopathological evaluation.

Figure 1. Distribution of patients by clinical and pathological evaluation.

clinically negative in the clinical axillary examination had involvement in the AP (OR = 3.44; 95%CI 1.92–6.16; p <0.0001) (Table 1).

Regarding the level of axillary involvement, according to the TNM staging system, 44.90% of the patients with a clinically positive examination were classified as N1 during the AP, and 20.40% were classified as N3. Among the patients who had a negative clinical examination with axillary anatomopathological involvement (false-negative), 71.43% were classified as N1 and 10.71% as N3. Predominance of four or more involved lymph nodes in the AP of patients with a clinically positive axilla on physical examination was observed (OR = 11.22; 95%CI 5.8–21.6) (Table 2).

DISCUSSION

In the present study, it was observed that 57.84% of the patients had a positive axillary clinical staging, but 16.95% had negative histopathological result. A similar result was found by Lanng et al.[5], in which 16.9% of the patients with palpable lymph nodes were histologically negative. However, these false-positive rates were lower than the National Surgical Adjuvant Breast and Bowel Project (NSABP) 4, in which 30% of the lymph nodes considered to be clinically positive had no metastasis upon histological examination[6], and the study performed at the Memorial Sloan Kettering Cancer Center (MSKCC)[4], in which the clinical examination failed in 41% of the cases. In the present study, the false-negative was high (65.12%), while the positive predictive value (PPV) was 83.51%, the negative predictive value (NPV) was 34.88%, and the accuracy was 62.75%. The results are similar to those of Lanng et al.[5], with a NPV of 38.5% and PPV of 84.4%[5]. In the present investigation, we observed an unnecessary axillary lymph node dissection in 16.95% of the cases, due to SLNB being contraindicated.

71.43% of the patients with negative clinical examination with axillary histopathological involvement, *i.e.*, the false-negatives, were classified as N1, and only 10.71% were classified as N3. These data are important for the study principles of the American College of Surgeons Oncology Group (ACOSOG) Z0011, as the majority of patients with clinically negative axilla (71.43%) was classified as N1 and could benefit from a resection of only up to three lymph nodes, if only one or two sentinel lymph nodes were involved, and thus not altering the overall survival rate or local recurrence[7], showing the correlation of axillary clinical evaluation with lymph node tumor load.

Finally, the majority of patients with anatomic pathological axillary involvement showed correlation with tumor grade, size, location and angiolymphatic invasion (Table 3).

Table 2. Level of axillary involvement.

Positive axilla AP (n=77)	Clinically positive axilla n (%)	Clinically negative axilla n (%)	Total n (%)	OR (95%CI)	value
N1	22 (52.3)	20 (47.7)	42 (100.0)	1.17 (0.67–2.04)	ns
N2	17 (77.3)*	5 (22.7)	22 (100.0)	11,22 (5.8–21.6)	<0.0001
N3	10 (77.0)*	3 (23.0)	13 (100.0)	11.22 (5.8–21.6)	<0.0001

AP: anatomopathological evaluation; OR: *odds ratio*; 95%CI: 95% confidence interval; ns: not significant; *statistically significant (p <0.0001) using Fisher's exact test.

Table 3. Clinical and pathological factors and axillary involvement.

	Positive axilla AP n (%)	Negative axilla AP n (%)	OR (95%CI)	p
Age				
<50	21 (84.0)**	4 (16.0)	27.56 (12.94–58.72)	<0.0001
≥50	56 (72.7)**	21 (27.3)	7.31 (3.91–13.65)	<0.0001
Tumor size				
3–3.99 cm	37 (67.0)**	18 (33.0)	4.12 (2.28–7.43)	<0.0001
4–5 cm	40 (85.0)**	7 (15.0)	32.11 (14.77–69.80)	<0.0001
Angiolymphatic invasion				
Yes	34 (81.0)**	8 (19.0)	18.17 (8.96–36.85)	<0.0001
No	42 (71.0)**	17 (29.0)	5.99 (3.25–11.04)	<0.0001
No information	1 (100.0)**	–	–	<0.0001
Histological grade				
1	–	1 (100.0)	–	<0.0001
2	23 (69.7)**	10 (30.3)	5.44 (2.97–9.97)	<0.0001
3	54 (79.4)**	14 (20.6)	14.15 (7.16–27.95)	<0.0001
Nuclear grade				
1	–	1 (100.0)	–	<0.0001
2	16 (61.5)*	10 (38.5)	2.66 (1.50–4.71)	0.0011
3	61 (81.3)**	14 (18.7)	18.17 (8.96–36.85)	<0.0001
Immunohistochemistry				
Luminal A/B	52 (74.3)**	18 (25.7)	8.10 (4.30–15.24)	<0.0001
Triple -	5 (55.5)	4 (44.4)	1,62 (0.92–2.83)	ns
HER-2 +	8 (100)**	–	–	<0.0001
Hybrid	9 (90.0)**	1 (10.0)	81 (32.15–204.1)	<0.0001
No information	3 (60.0)*	2 (40.0)	2.25 (1.27–3.96)	0.0071

AP: anatomopathological evaluation; OR: *odds ratio*; 95%CI: 95% confidence interval; ns: not significant; *statistically significant (p≤0.01) by Fisher's test; **statistically significant (p≤0,0001) using Fisher's exact test.

CONCLUSION

Clinical axillary evaluation as a criterion for the indication for SLNB is imprecise. Clinical examination of the axilla is highly susceptible to false-positive and negative results and is insufficient for the justification of axillary lymphadenectomy. A better evaluation of the prediction of lymph node involvement is important, considering some clinical and pathological risk factors in patients with suspicious lymph nodes.

REFERENCES

1. 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;11:927-33.
2. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst. 2006;98:599-609.
3. Harlow SP, Weaver DL. Management of the regional lymph nodes in breast cancer. UpToDate. 2014.
4. Specht MC, Fey JV, Borgen PI, Cody HS 3rd. Is the clinically positive axilla in breast cancer really a contraindication to sentinel lymph node biopsy? J Am Coll Surg. 2005;200:10-4.
5. Lanng C, Hoffmann J, Galatius H, Engel U. Assessment of clinical palpation of the axilla as a criterion for performing the sentinel node procedure in breast cancer. Eur J Surg Oncol. 2007;33:281-4.
6. Fisher ER, Sass R, Fisher B. Pathologic findings from national surgical adjuvant project for breast cancers (Protocol No.4) Discriminants for tenth year treatment for line. Cancer. 1984;53(3):712-23.
7. Giuliano A, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, et al. Locoregional recurrence after Sentinel Node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z 0011 randomized trial. Ann Surg. 2010;252:426-33.

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INTRAPAPILLARY DUCT DILATION: A NEW ULTRASONOGRAPHY SIGN

Dilatação ductal intrapapilar: um novo sinal ultrassonográfico

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ABSTRACT

Objective: To evaluate a not yet described ultrasound finding, the dilation of the intra-papillary portion of the lactiferous duct in patients with or without abnormal nipple discharge **Methods:** 24 patients with pathological nipple discharge and intrapapillary duct dilation and 1,255 asymptomatic patients (control group) were studied. **Results:** Just one asymptomatic patient had intrapapillary duct dilation. Among the symptomatic patients, 19 were biopsied: ten with exclusively percutaneous approach, six with exclusively surgical approach, and three with an initial percutaneous and then a surgical approach. There was one invasive carcinoma and two carcinomas in situ (15.8% of the biopsied patients). In 11 patients, a papilloma was found, three of them with atypia. In one patient, ultrasonography identified intrapapillary extension of microcalcifications, and another patient a changed duct diametrically opposite to the duct which had a trigger point. In these two patients, the examination changed the treatment strategy. In two other patients, an extra-papillary finding was identified only after the intrapapillary duct dilation has been encountered. **Conclusion:** The intrapapillary duct dilation is a new ultrasonography sign that adds sensitivity to the evaluation of the patient with pathological nipple discharge, besides helping to find the lesion and to guide the treatment. Further research is needed to determine its prevalence and its positive and negative predictive values for cancer, atypia and papilloma.

KEYWORDS: breast ultra-sonography; nipple discharge; mammary duct ectasia; papilloma; breast neoplasms.

RESUMO

Objetivo: Avaliar um achado de ultrassonografia inédito (dilatação intrapapilar do duto lactífero) em pacientes portadoras de fluxo papilar patológico e em pacientes assintomáticas. **Métodos:** Foram estudadas 24 portadoras de fluxo papilar patológico e dilatação ductal intrapapilar e 1.255 pacientes assintomáticas (grupo controle). **Resultados:** Apenas uma paciente assintomática apresentou dilatação ductal intrapapilar. Entre as pacientes sintomáticas, 19 foram biopsiadas, 10 com abordagem exclusivamente percutânea, 6 com abordagem exclusivamente cirúrgica e 3 com abordagem inicialmente percutânea e depois cirúrgica. Houve um carcinoma invasor e dois carcinomas *in situ* (15,8% das pacientes biopsiadas). Em 11 pacientes foi encontrado papiloma, 3 deles com atipias. Em uma paciente a ultrassonografia identificou extensão intrapapilar de microcalcificações e em outra, um duto alterado diametralmente oposto ao duto com sinal do gatilho clínico. Nessas duas pacientes o exame mudou a estratégia de tratamento. Em duas pacientes, um achado extrapapilar só foi identificado após o encontro da dilatação ductal intrapapilar. **Conclusão:** A dilatação ductal intrapapilar é novo sinal ultrassonográfico que agrega sensibilidade à avaliação da paciente com fluxo papilar patológico, além de ajudar a encontrar a lesão e a orientar o tratamento. São necessárias pesquisas adicionais para determinar sua prevalência e seus valores preditivos positivo e negativo para câncer, atipias e papilomas.

PALAVRAS-CHAVE: ultrassonografia mamária; derrame papilar; papiloma; neoplasias da mama.

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INTRODUCTION

Nipple discharge is considered pathological when it is unilateral and has a watery or bloody appearance [1]. In addition to being an uncomfortable symptom, the presence of pathological nipple discharge brings the concern of significant breast disease, more commonly papilloma, but even carcinoma, in some cases[2].

The propaedeutic methods available to investigate nipple discharge include oncotic cytology of the secretion, imaging techniques such as mammography, ductography, ultrasonography andmagnetic resonance imaging (MRI) and even endoscopic techniques, like ductoscopy. However, all these methods have limited sensitivity, specificity and/or availability. Given these limitations, new concepts and features that may help the approach of the pathological nipple discharge patients are desirable, especially if they do not have additional costs or poor availability.

This article presents a finding unpublished up to now: the identification of a dilated fluid-filled intrapapillary portion of the lactiferous duct. This sign seems to be important in the diagnosis of the pathological nipple discharge, as a marker of a relevant duct disease as much as an assistance to find the diseased duct. This article describes this finding and preliminary results of its identification.

METHODS

We identified for the first time in 2010 the intrapapillary duct dilation, in a patient with a dark-color unilateral nipple discharge, which gave ground for suspecting of the presence of red blood cells (Figure 1). The oncotic cytology found proliferative cells suggesting papilloma. The ultrasonography showed a dilated duct containing liquid inside the nipple. At that time, we did not know if this finding had any relation to the patient's clinical profile.

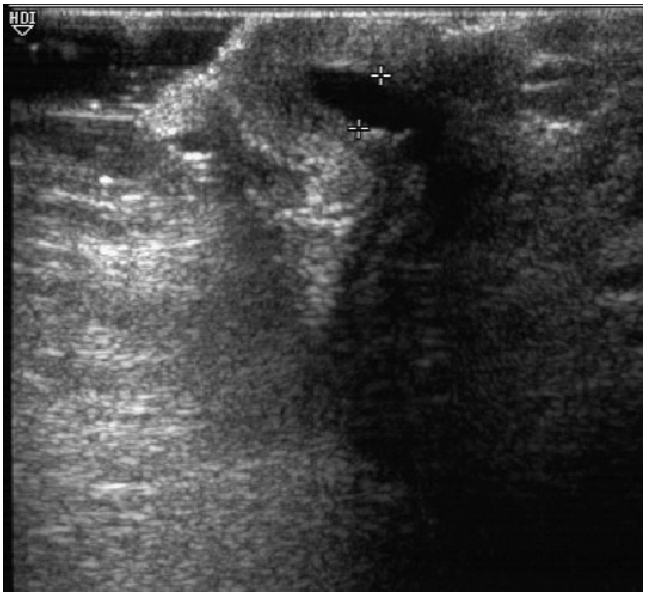

Figure 1. Dilation containing liquid from an intrapapillary segment of a lactation duct.

A long time has passed before we saw this finding again. In 2016, we identified the intrapapillary duct dilation in a patient with a frankly bloody unilateral nipple discharge. This second identification drew our attention to the potential diagnostic value of this finding. So, we began to look for it systematically in all patients with pathological nipple discharge. Until we completed the inclusion of cases for this article (March 2017), we found intrapapillary duct dilation in 24 patients. This specific group of patients was the object of this study.

The presence of other extra-papillary imaging alterations was studied by ultrasonography, mammography or MRI. When the biopsy was performed the biopsy method and the histopathological findings were also object of study.

Various types of ultrasonography devices were used, all of them with high-frequency linear transducers: Voluson 630, Voluson PRO and Logiq S8 (GE Healthcare, Chicago, Illinois, Unites States) and HDI 5000 (ATL, Bothell, Washington, Unites States).

As a control group, we systematically examined the papilla of 1,255 asymptomatic women on consecutive breast ultrasonography examinations over a period of 10 months.

RESULTS

Among 1,255 patients who did not present nipple discharge (control group), just one had intrapapillary duct dilation, without any other finding.

Among the 24 patients with intrapapillary duct dilation, the ages ranged from 29 to 51 years old, with average of 54 and median of 51 years old.

Table 1 shows a summary of the extra-papillary and histopathological findings in patients with intrapapillary duct dilation, as well as the biopsy method used when the patient underwent biopsy.

Twenty-one patients had an extra-papillary associated finding, including nodule, duct ectasia with or without internal solid areas (Figures 2 and 3), duct thickening (Figure 4), or microcalcifications. In two patients, these extra-papillary finding were only detected after the identification of intrapapillary duct dilation. Only three patients had no other findings.

In one patient, there were two ducts with parietal thickening of diametrically opposite orientation. One of them was related to a trigger point, and the other one continued with the dilated duct segment within the papilla. We decided to recommend the excision of these two ducts, guided by the placement of two guidewires under ultrasonographic guidance (Figure 5), and the histopathological in this case showed epithelial proliferation in both specimens.

In one patient, intraductal calcifications were very apparent on ultrasonography which had also been seen on mammography. However, due to mammography compression, the microcalcifications appeared to be outside of the papilla, but the ultrasonography showed that they penetrated inside the papilla along with the lumen of the duct (Figure 6).

Table 1. Extra-papillary findings, histopathological results and biopsy method (when it is performed) in patients with intrapapillary duct dilation.

Patient	Age (years)	Result	Biopsy method	Additional image findings
1	44	Papilloma without atypia	Fine needle biopsy	Small solid lesion filling the duct
2	60	Ectasia, fibrosis	Mammotomy	Branched ducts with solid content
3	50	CDIS	Mammotomy	Thickened ducts and small nodules
4	36	No biopsy	No biopsy	Duct parietal thickening, healed with clinical treatment, characterizing galactoforitis
5	40	Papilloma with ADH	Mammotomy, after surgery	Branched complex lesion
6	29	Atypical papilloma	Biopsy of fragments, after surgery	Branched intraductal lesion
7	66	No biopsy	No biopsy	Prominent duct ectasia with internal echoes, probably representing solid content
8	43	Galactoforitis	Mammotomy	Extensive and branched intraductal lesion
9	48	No biopsy	No biopsy	Extensive intraductal lesion
10	48	Papilloma without atypia	Mammotomy	Intraductal solid lesion
11	44	Galactoforitis	Mammotomy	Discrete intraductal solid lesion
12	72	No biopsy	No biopsy	No other lesion
13	47	Papilloma without atypia	Surgery	Thickened duct with solid content
14	73	Papilloma without atypia	Mammotomy, after surgery	Solid intraductal content and nodule
15	73	Papilloma without atypia	Mammotomy, after surgery	Duct with solid content and nodules coming out of the duct
16	48	Invasive carcinoma	Fragment biopsy	Suspect lesion solid voluminous and microcalcifications
17	51	Papilloma without atypia	Mammotomy	No other lesion
18	58	No biopsy	No biopsy (recommended control)	No other lesion
19	61	Stromal fibrosis	Surgery	Duct with extensive vascularized solid area
20	62	Epithelial proliferation	Surgery	Thickened duct 12h; lesion 6h. Double needling.
21	51	Papilloma without atypia	Surgery	No other lesion.
22	63	Atypical papilloma	Surgery	Injuries type papiloform
23	55	Papilloma without atypia	Surgery	Small papillary and peripapillary intraductal lesion
24	85	High-degree CDIS	Mammotomy	Skinned edema, nipple retraction

CDIS: carcinoma ductal *in situ*; ADH: atypical duct hyperplasia.

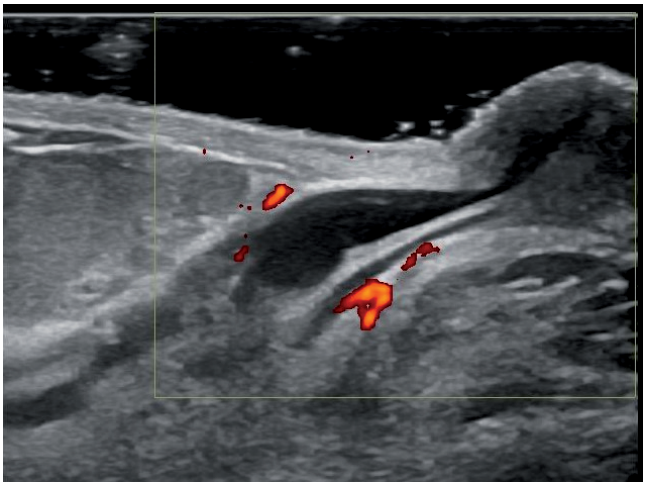

Figure 2. Intrapapillary duct dilation and solid intraductal lesion.

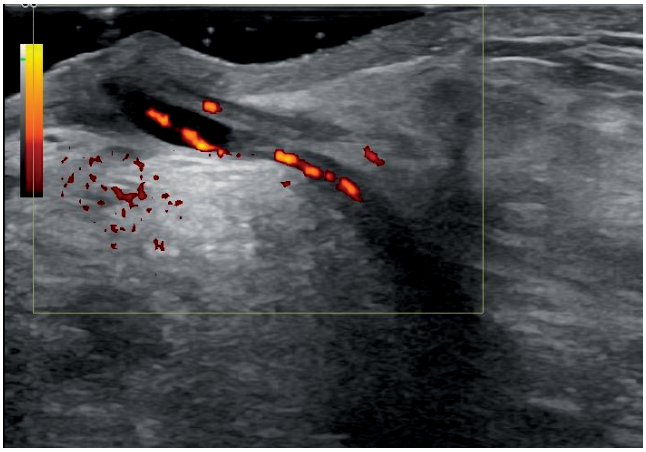

Figure 3. Another patient, with Doppler confirming the solid character of the intraductal content.

Five patients did not undergo biopsy. Three of them had no associated lesions and received a clinical recommendation of follow-up. In the other two patients, there were extra-papillary findings that led to biopsy recommendation, but the patients refused the biopsy.

Of the 19 patients who were submitted to biopsy, 13 initially underwent a percutaneous approach: 10 patients by vacuum-assisted biopsy (in three of them a complementary surgery was necessary), two by spring-loaded core biopsy (one of them required complementary surgery), and one by fine needle aspiration. In six patients, the initial approach was surgical. Therefore, among the patients submitted to the tissue diagnosis, surgery was performed in nine of them, while the other ten received an exclusively percutaneous procedure.

There was one case of invasive carcinoma, with exuberant extra-papillary findings, and two cases of duct carcinoma *in situ*, with discrete extra-papillary finding (15.8% of the biopsied patients).

In three patients, atypia was found, always inside a papilloma. In eight patients, papilloma without atypia was encountered.

There were also two diagnoses of fibrosis and three diagnoses of galactoforitis (two with histopathological confirmation and one presumed by clinical evolution) (Figure 7).

In the patients who were also investigated by MRI, the intra-papillary duct dilation appeared as an intrapapillary tubular structure with high signal on T2.

Several patients were also investigated by mammography. Some patients presented nonspecific retro-papillary tubular densities (which was compatible to duct ectasia). Several patients had no one mammographic finding. One patient had suspicious microcalcifications and densities.

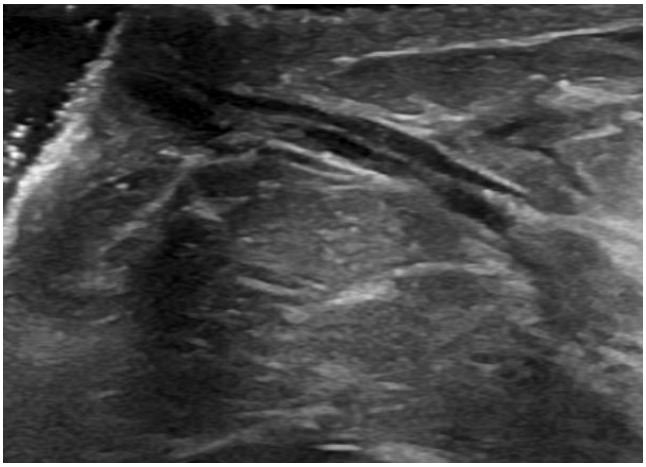

Figure 4. Parietal thickening of ducts in continuity with intrapapillary duct dilation.

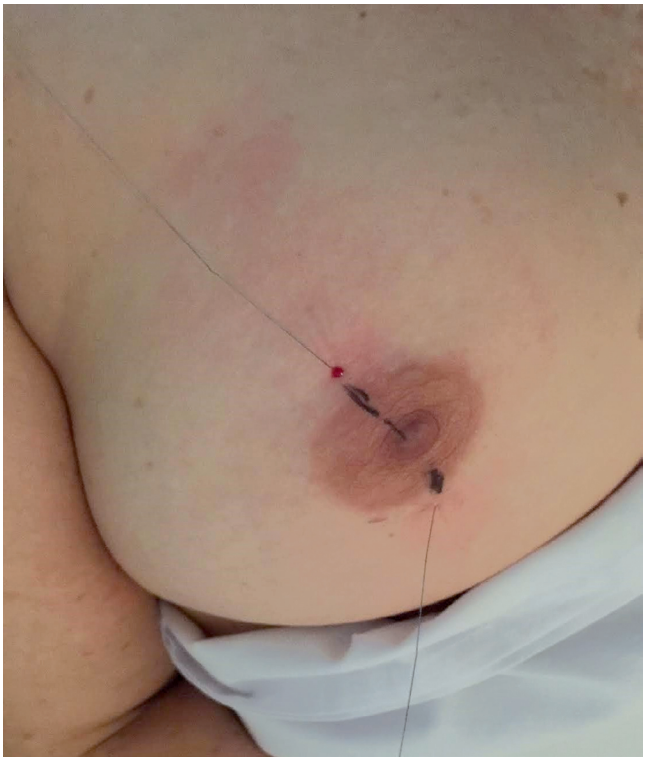

Figure 5. Guidewires in ducts, one of them related to the clinical sign of the onset, and the other one containing ultra-sonographic alteration, seen only after the identification of the intrapapillary dilation.

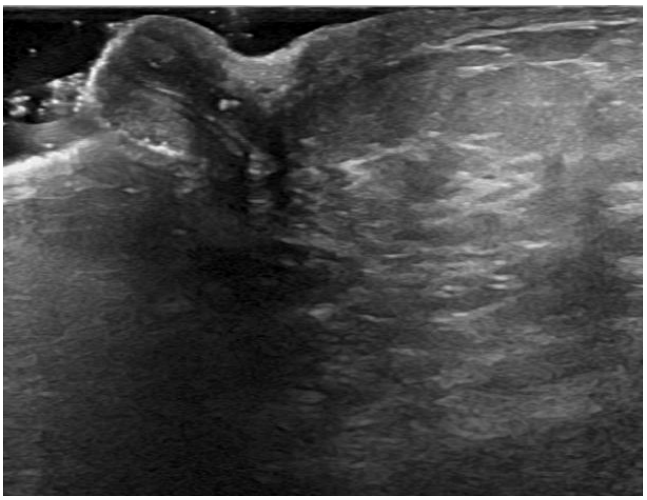

Figure 6. Intra-papillares microcalcifications.

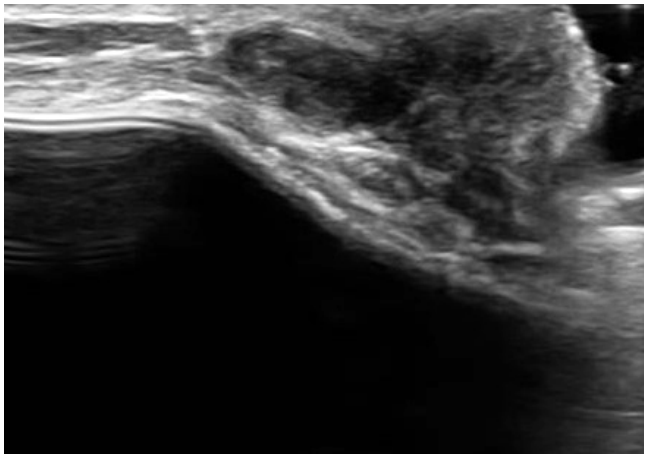

Figure 7. Galactoforitis was improved with antibiotic.

DISCUSSION

The diagnostic approach of patients with pathological nipple discharge can be difficult, and the imaging tests are often normal[1,3]. The cytopathic examination of the secretion discharged has high rates of inconclusive results and sub-ideal specificity[4]. The ductography, besides having low specificity[5], has been falling into disuse[6] and nowadays it has limited availability. Some studies have shown good accuracy in techniques such as ductoscopy[3] and duct washing cytology[5], however, besides invasive, these techniques are rarely available[7]. The MRI has been used in some centers to evaluate papillary discharge, and one author found that the positive predictive value for carcinoma of this symptom falls from 5.7 to 4% if the resonance does not show suspicious changes[8]. He concluded that these data may enable an approach that carries the follow-up of these patients, but 4% is still slightly above of the 2% positive predictive value normally accepted to assign the category BI-RADS 3 to findings in asymptomatic patients, showing that its conclusion still deserves further reflection.

The majority of the patients with pathological nipple discharge do not have any relevant disease in the breasts, but a subgroup of these patients may present potentially serious diseases[5,9]. When in the imaging examinations there are no findings, the doctor must decides between adopting an expectant management or resecting the retroareolar duct as a way to eliminate the symptom and also to investigate its etiology. The blind excision of retroareolar ducts, however, brings the risk of not withdrawing a peripherally situated lesion, interrupting the exteriorization of the discharge produced by this lesion and potentially delaying the diagnosis of a malignant disease.

With a specific diagnosis of the diseased duct, the surgical treatment can be directed and less aggressive. In some cases, with small size lesions, a percutaneous approach might also be possible[10]. This percutaneous approach is supported by our data.

The ultrasound sign described herein may be difficult to identify previously when it is not known. In our experience, we spent six years without identifying it again after the first time, because we were not aware of its potential importance. It is probably right to say that careful examination of the nipple is an often-neglected step in breast ultrasonography. This step requires special maneuvers, such as using large amounts of gel (Figures 2 and 3), or laterally compressing the papilla to rectify the ducts (Figure 6), as described by Stavros[11] and da Costa et al.[12].

When we specifically look for it, the intrapapillary duct dilation is easy to identify. Moreover, our data shows that it helps to find out the diseased duct and that it seems to be frequent in cases of pathological nipple discharge.

In many of our patients, there was a relevant extra-papillary lesion; in three of them the intrapapillary duct dilation helped to find out this lesion, suggesting that it is not just a diagnostic curiosity, but a way to increase the sensitivity of the breast ultrasonography.

We did not find out any previous description of this sign in the literature. There are some pictorial essays on duct ectasias and nipple lesions in the literature, and one of them shows an intraductal papillary dilation containing liquid, but it does not recognize this situation as an important diagnostic element[13].

The three cases of galactoforitis were an interesting finding. This diagnosis is not very well remembered usually in the context of the patient with pathological nipple discharge.

CONCLUSION

The intrapapillary dilation of a duct segment is a new ultrasonography sign that adds diagnostic value to the exam without increasing its costs. It helps to sort relevant diseases in women with pathological nipple discharge and to find out the specific site of the cause of the discharge. Its identification may increase the sensitivity of the breast ultrasonography helping guide the treatment, avoiding unnecessary surgeries and reducing the size of surgeries.

Additional research is needed to determine its prevalence in patients with pathological nipple discharge, besides to its positive and negative predictive values for malignant diseases, atypia, papilloma and galactoforitis.

REFERENCES

1. Richards T, Hunt A, Courtney S, Umeh H. Nipple discharge: a sign of breast cancer? Ann R Coll Surg Engl. 2007;89:124-6. https://doi.org/10.1308/003588407X155491
2. van Gelder L, Bisschops RH, Menke-Pluymers MB, Westenend PJ, Plaisier PW. Magnetic resonance imaging in patients with unilateral bloody nipple discharge; useful when conventional diagnostics are negative? World J Surg. 2015;39(1):184-6. https://doi.org/10.1007/s00268-014-2701-1
3. Fisher CS, Margenthaler JA. A look into the ductoscope: its role in pathologic nipple discharge. Ann Surg Oncol. 2011;18(11):3187-91. https://doi.org/10.1245/s10434-011-1962-2
4. Gupta RK, Gaskell D, Dowle CS, Simpson JS, King BR, Naran S, et al. The role of nipple discharge cytology in the diagnosis of breast disease: a study of 1948 nipple discharge smears from 1530 patients. Cytopathology. 2004;15:326-30. https://doi.org/10.1111/j.1365-2303.2004.00169.x

5. Hou MF, Tsai KB, Ou-Yang F, Lin HJ, Liu CS, Chai CY, et al. Is a one-step operation for breast cancer patients presenting nipple discharge without palpable mass feasible? Breast. 2002;11:402-7. https://doi.org/10.1054/brst.2002.0441

6. Nazario ACP, Rego MF, Oliveira VM. Nódulos benignos da mama: uma revisão dos diagnósticos diferenciais e conduta. Rev Bras Ginecol Obstet. 2007;29(4):211-9. http://dx.doi.org/10.1590/S0100-72032007000400008

7. Mokbel K, Escobar PF, Matsunaga T. Mammary ductoscopy: current status and future prospects. Eur J Surg Oncol. 2005;31:3-8. https://doi.org/10.1016/j.ejso.2004.10.004

8. Bahl M, Gadd MA, Lehman C. Diagnostic Utility of MRI After Negative or Inconclusive Mammography for the Evaluation of Pathologic Nipple Discharge. AJR Am J Roentgenol. 2017;209:1404-10. https://doi.org/10.2214/AJR.17.18139

9. Seow JH, Metcalf C, Wylie E. Nipple discharge in a screening programme: imaging findings with pathological correlation. J Med Imaging Radiat Oncol. 2011;55(6):577-86. https://doi.org/10.1111/j.1754-9485.2011.02294.x

10. Torres-Tabanera M, Alonso-Bartolomé P, Vega-Bolivar A, Sánchez-Gómez SM, Lag-Asturiano E, Sainz-Miranda M, et al. Percutaneous microductectomy with a directional vacuum-assisted system guided by ultrasonography for the treatment of breast discharge: experience in 63 cases. Acta Radiol. 2008;49(3):271-6. https://doi.org/10.1080/02841850701769793

11. Stavros AT. Breast anatomy: the basis for understanding sonography. In: Stavros AT. Breast ultrasound. Philadelphia: Lippincott Williams & Wilkins; 2004. p.85-9.

12. Da Costa D, Taddese A, Cure ML, Gerson D, Poppiti R, Esserman LE. Common and Unusual Diseases of the Nipple Areolar Complex. RadioGraphics. 2007;27:S65-77. https://doi.org/10.1148/rg.27si075512

13. Eiada R, Chong J, Kulkarni S, Goldberg F, Muradali D. Papillary Lesions of the Breast: MRI, Ultrasound, and Mammographic Appearances. AJR Am J Roentgenol. 2012;198:264-71. https://doi.org/10.2214/AJR.11.7922

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INVASIVE LOBULAR CARCINOMAS TREATED AT HOSPITAL DE CLÍNICAS OF UFPR: INCIDENCE, CHARACTERISTICS AND CLINICAL OUTCOME

Carcinomas lobulares invasores de mama tratados no Hospital de Clínicas da UFPR: incidência, características e evolução clínica

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ABSTRACT

Objective: The aim of this study is to depict the clinical and epidemiological profile of patients treated for invasive lobular carcinoma (ILC) at Hospital das Clínicas of Universidade Federal do Paraná (HC-UFPR) over the course of ten years and to evaluate the variation of ILC dimensions on imaging exams by comparing them to real-size lesions identified in surgical specimens. **Methods:** Patients undergoing breast surgical procedures at HC-UFPR from 2005 to 2014 were selected. Out of these, 36 were diagnosed with ILC and had their medical files sought after clinical, epidemiological, therapeutic and prognosis characteristics. The variance of tumor sizes in imaging methods and anatomopathological descriptions were also studied. **Results:** Patients' mean age at diagnosis was 59.6 years. Most of them were classified as clinical stages II (40%) and III (26.7%) by the time they were diagnosed. The majority of tumors were HER2 negative (77.2%) and estrogen-receptor positive (90%). The surgical treatment was radical in 74.2% of the cases. 31.4% of the patients underwent both mammography and ultrasonography screening and 45.7% underwent only one of them. None of the patients were submitted to magnetic resonance imaging (MRI). **Conclusion:** Data found about patients with invasive lobular carcinoma at HC-UFPR is in accordance with the medical literature, including incidence rates and tumor characteristics. The variance of tumor sizes in imaging exams and surgical specimen was not statistically significant.

KEYWORDS: lobular carcinoma; breast neoplasms; histology; ductal carcinoma; medullary carcinoma.

RESUMO

Objetivo: O estudo busca caracterizar o perfil clínico epidemiológico referente às pacientes tratadas por carcinoma lobular invasor de mama (CLI) no Hospital de Clínicas da Universidade Federal do Paraná (HC-UFPR) em um período de dez anos e avaliar as variações das dimensões dos CLI nos exames de imagem quando comparadas ao real tamanho das lesões identificadas nas peças de anatomia patológica. **Métodos:** Foram selecionadas pacientes submetidas a procedimentos cirúrgicos de mama no HC-UFPR entre os anos de 2005 e 2014, dentre as quais 36 apresentaram diagnóstico de CLI. Seus prontuários foram analisados para avaliação de características clínicas, epidemiológicas, terapêuticas e prognósticas. Também foi avaliada a discrepância dos valores de tamanho do tumor em métodos de imagem em relação ao descrito nos laudos anatomopatológicos. **Resultados:** As pacientes com diagnóstico de CLI tinham média de idade no diagnóstico de 59,6 anos. O diagnóstico foi feito, em sua maioria, nos estádios clínicos II (40%) e III (26,7%). Houve maior negatividade (77,2%) para HER2 e positividade (90%) para receptor de estrógeno. O tratamento cirúrgico foi radical em 74,2% das pacientes. Em exames de imagem, 31,4% das pacientes realizaram mamografia e ultrassonografia em conjunto, 45,7% fizeram apenas um dos exames e nenhuma realizou ressonância magnética. **Conclusão:** Observou-se que a casuística de patologias mamárias do HC-UFPR está de acordo com a literatura em relação à incidência e às características próprias dos CLI. A análise da discrepância dos tamanhos dos tumores em exames de imagem em relação às peças cirúrgicas não obteve resultados significativos estatisticamente.

PALAVRAS-CHAVE: carcinoma lobular; neoplasias da mama; histologia; carcinoma ductal; carcinoma medular.

Study carried out at Hospital de Clínicas of Universidade Federal do Paraná – Curitiba (PR), Brazil.
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INTRODUCTION

Breast cancer, excluding non-melanoma skin cancer, is the most common neoplasm among women around the world and also the one presenting the highest mortality rate[1]. According to the National Cancer Institute (INCA), breast cancer was the most common among females in 2016, with estimated 57,960 new cases that year[2]. Most of them are placed in the category of invasive breast cancer, which is typically classified according to histology as invasive ductal carcinoma, the most frequent type and accounting for about 75% of all cases, and as special subtype of breast carcinoma, mainly represented by invasive lobular carcinoma (ILC)[3]. Although these are within the same disease's spectrum, there is an undeniable heterogeneity between the mentioned entities. Such differences are related to risk factors, clinical presentation and prognosis, as they vary according to subtypes of invasive breast carcinomas[4].

ILC contributes with about 10 to 15% of all cases of breast cancer in the West, and its incidence increased significantly from the 1970s to the 2000s. Postmenopausal hormone replacement therapy has been identified as the primary cause of this increase, while the improvement in methods of detection has a supportive role in this scenario[3]. With the decrease in indications for hormone therapy at the beginning of the millennium, the reduction in ILC incidence occurred parallel[5,6]. However, since 2004, the number of cases has increased again for reasons not yet elucidated[7,8].

Some of the major risk factors linked to the development of ILC are: advanced age at first child delivery, late menopause, and postmenopausal hormone replacement therapy. Positive family history of malignancy in first-degree relatives also poses an increased risk of developing ILC in life[9-12].

Clinically, when compared to the non-special type of breast carcinoma, ILC presents as a larger, well-differentiated tumor at diagnosis in patients with advanced age, being frequently associated with multifocality and positive lymph node involvement, with typical molecular profile positive for estrogen receptors (ER) and negative for HER2[13-15].

Histologically, the disease is characterized by small, uniform cells grouping that invade the breast stroma in a linear clustering pattern, also referred to as "in-line" clustering. These characteristics increase technical difficulty to detect ILC upon physical examination, mammography and other imaging methods available for screening and diagnosis of breast cancer. For this reason, a much larger tumor is often found upon surgical treatment or pathological anatomy compared to what has been predicted by previous imaging tests[16]. In order to reduce this type of unexpected findings during surgeries, more accurate imaging tests such as magnetic resonance imaging (MRI) are recommended in surgical planning for ILC patients[17].

Despite the technical difficulties to early diagnose lobular carcinomas by imaging methods, the survival and disease-free time in ILC was shown to be similar or better compared to breast ductal carcinomas, in addition to many studies indicating lower rates of local recurrence in the special subtype of breast carcinoma[16,18].

This study tries and depicts the clinical and epidemiological characteristics of patients treated for ILC at Hospital de Clinicas of Universiade Federal University do Paraná (HC-UFPR) over a period of 10 years, aiming to identify patterns and peculiarities of its manifestation, which has presented several variations of incidence and profile over the decades. In addition, variations in ILC dimensions upon imaging examinations and compared to the real size of lesions identified in post-surgical pieces of pathological anatomy are also analyzed.

METHODS

Patients submitted to breast surgical procedures at the HC-UFPR between 2005 and 2014 were retrospectively selected. The eligibility criteria were: females of all ages submitted to breast surgery of any nature at the HC-UFPR in the period established. Patients who underwent breast procedures with esthetic purposes or did not meet all inclusion criteria were excluded. All cases of breast lesions found in biopsy records of the HC-UFPR Pathology Service from 2005 to 2014 were evaluated for patient selection. Reports were then assessed case by case to maintain the epidemiological records of the case series in the hospital and in search for cases of ILC.

There were 1,501 cases of breast lesions in the period, with their anatomopathological reports recorded in spreadsheet. Among these cases, 36 were ILC, one of the patients being excluded from due to absence of medical records at the Medical Archive Service; 35 cases of ILC were selected. These patients had their charts analyzed for detailed data collection and evaluation of tumor specific characteristics, family and past history, therapeutic approach, clinical evolution and survival. Discrepancies in tumor size found in mammography, ultrasonography (US) or MRI compared to the size described in pathological anatomy reports were also evaluated.

Tumor size was determined by its larger diameter when more than one dimension was described. Disease-free interval (DFI) and survival rates post-treatment were used as a parameter to assess patient survival. The DFI was calculated from day of diagnosis to day of first recurrence, while survival after treatment comprised the period until the last visit. Over the 10 years studied, the service lost eight patients to follow-up, and their DFI and survival rate were calculated based on the date of their last visit. All data collected were input to an Excel® 2013 spreadsheet.

The software R DEVELOPMENT CORE TEAM® was used for statistical analysis and inferential statistics tests applied were Kruskal-Wallis test and Spearman's correlation, with results considered statistically significant when $p \leq 0.05$. The study was approved by the Research Ethics Committee of HC-UFPR.

RESULTS

The epidemiological analysis of this breast cancer case series of HC-UFPR showed that, from 1,501 cases recorded between 2005 and 2014, 908 (60.5%) had benign findings at biopsy and 593 (39.5%) tested positive for malignancy. From malignancy cases, 505 (85.01%) were invasive ductal carcinomas, 36 (6.07%) were ILC and 20 (3.37%) were mixed carcinomas. Results are detailed in Graph 1.

Patients diagnosed with ILC had mean age of 59.6 years at diagnosis, mean age of menarche of 12.75 years, mean age of menopause of 47.59 years, mean number of children of 2.2 and negative family history for breast cancer in most cases (77.1%). The diagnosis was mainly concluded at clinical stages II (40%) and III (26.7%). The full set of results regarding the profile of patients are compiled in Table 1. As for the molecular characteristics of ILC tumors, 77.1% of cases were HER2 negative (0+ and 1+), but progesterone (PR) and estrogen (ER) receptors were positive in most cases (70 and 90%, respectively). Radical mastectomy was the surgical procedure of choice for most patients (74.2%), clinical therapy with hormone therapy was indicated in 71.4% of cases and radiotherapy was applied in 60%. Tumor characteristics are listed in Table 2 and types of treatments are shown in Table 3.

Regarding the imaging tests used, 31.4% of the patients were submitted to mammography and US in combination, with most patients performing only one of the exams (45.7%). No patients included in the study had been submitted to MRI. Results on imaging tests are shown in Table 4. Inferential statistics was analyzed by correlation of survival after treatment against clinical stage (Graph 2A) and DFI against clinical stage (Graph 2B), with statistically significant results in both instances. Post-treatment survival versus tumor size upon pathologic biopsy (Graph 3A), DFI versus tumor size upon pathologic biopsy (Graph 3B), and tumor size at imaging versus tumor size upon pathologic biopsy (Graph 4) were not statistically significant.

DISCUSSION

The increase in incidence of ILC, as well as its clinical and therapeutic peculiarities require further studies like this one, aiming to evaluate its characteristics not only to improve understanding about its pathology, but also to help establish specific strategies to approach patients.

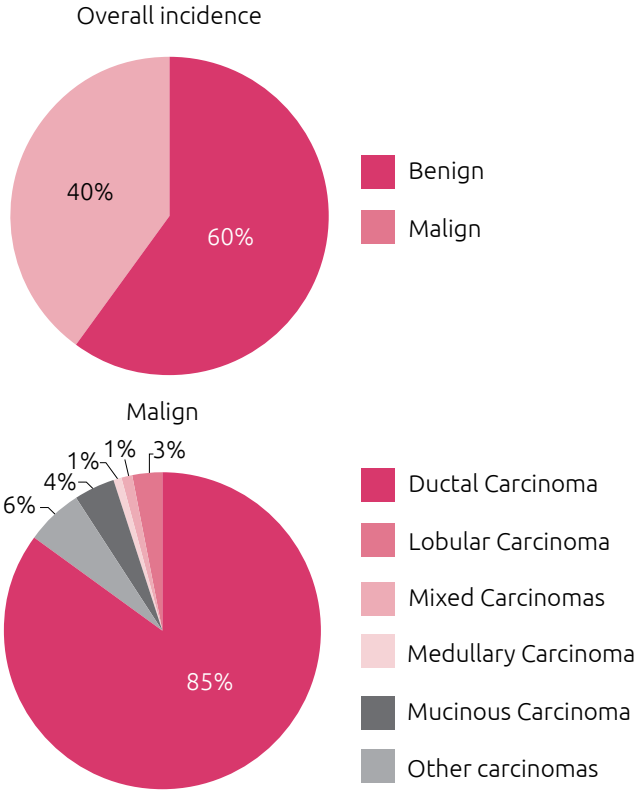
Of 596 biopsies positive for malignancy in the service, 36 resulted in ILC, totaling 6.07% of all cases. The prevalence of cases treated is consistent with the literature, which predicts a contribution of about 10% of breast malignancies by ILC, ranging from 5 to 15% in the series reported[4].

Mean age at diagnosis of ILC in patients studied was 59.6 years, which is consistent with previous reports stating that CLI predominantly affects patients aged 50 years or more[15]. The common involvement of menopausal patients is suggested to be associated with the lower aggressiveness of lobular lesions, whose proliferative indexes are usually low and postpone clinical manifestations[19]. Another hypothesis considered is that these patients would be more affected due to the late diagnosis of lobular lesions, as these are more difficult to perceive through screening imaging[20].

Positive family history of breast cancer was present in 22.9% of cases. In contrast, a study conducted in 2015 on 135 cases of ILC reported only 4.5% of cases with positive family history[21]. This difference is possibly related to the small number of cases assessed in our study, leading to a biased sample.

The quadrant of the breast most affected by ILC was superexternal (41.9%), which is consistent with other reports in the literature and classically attributed to the fact that it is the region of the breast with the highest concentration of mammary parenchyma, thus more prone to disease occurrence[22].

The most common clinical stages found in our study were II (40%) and III (26.7%), and the initial stages (I and II) together accounting for 50% of the cases. Another Brazilian study obtained similar results, with 57% of cases diagnosed in initial clinical stages[23]. However, international studies have shown a much more significant incidence of diagnoses at early clinical stages, suggesting a better and more comprehensive screening system[22].



Incidence of cases of breast cancer treated at HC-UFPR between 2005 and 2014.

Graph 1. Incidence of cases of breast neoplasms treated at HC-UFPR.

Table 1. Profile of patients with invasive lobular carcinoma.

		Absolute frequency	Relative frequency (%)
Breast cancer Family history*	Positive	8	22.9
	Negative	27	77.1
Associates systemic diseases**	Yes	18	51.4
	No	17	48.6
Laterality	Right	17	50.0
	Left	13	38.2
	Bilateral	4	11.7
Breast quadrant***	UOQ	13	41.9
	UIQ	2	6.4
	ISQ	2	6.4
	IIQ	2	6.4
	Central	5	16.1
	More than one local	7	22.5
Clinical stage	1	3	10.0
	2	12	40.0
	3	8	26.7
	4	7	23.3

General clinical data and previous history of patients with invasive lobular carcinoma of the breast treated at HC-UFPR between 2005 and 2014. *Only first-degree relatives were considered for family history; **systemic diseases considered were systemic arterial hypertension (SAH), diabetes mellitus (DM), obesity, smoking, alcoholism and thyroid disorders; ***UOQ: upper-outer quadrant, UIQ: upper-inner quadrant, ISQ: infero-sternal quadrant, IIQ: infero-internal quadrant.

Table 2. Tumor characteristics.

		Absolute frequency	Relative frequency (%)
HER2	0	24	68.6
	1+	3	8.6
	2+	6	17.1
	3+	2	5.7
ER*	Positive	27	90.0
	Negative	3	10.0
PR**	Positive	21	70.0
	Negative	9	30.0

Molecular characteristics of invasive lobular carcinoma of the breast treated at HC-UFPR between 2005 and 2014; *ER: estrogen receptor; **PR: progesterone receptor

Table 3. Treatment.

		Absolute frequency	Relative frequency (%)
Surgical treatment	Conservative	8	25.8
	Radical	23	74.2
Axillary approach	Sentinel lymph node	6	22.2
	Axillary emptying	17	62.9
	Both	4	14.8
Chemotherapy	Yes	20	57.1
	No	15	42.9
Hormone therapy	Sim	25	71.4
	NI*	10	28.6
Radiotherapy	Yes	21	60.0
	No	14	40.0

Therapeutic approach used in cases of invasive lobular carcinoma treated at HC-UFPR between 2005 and 2014; *not informed.

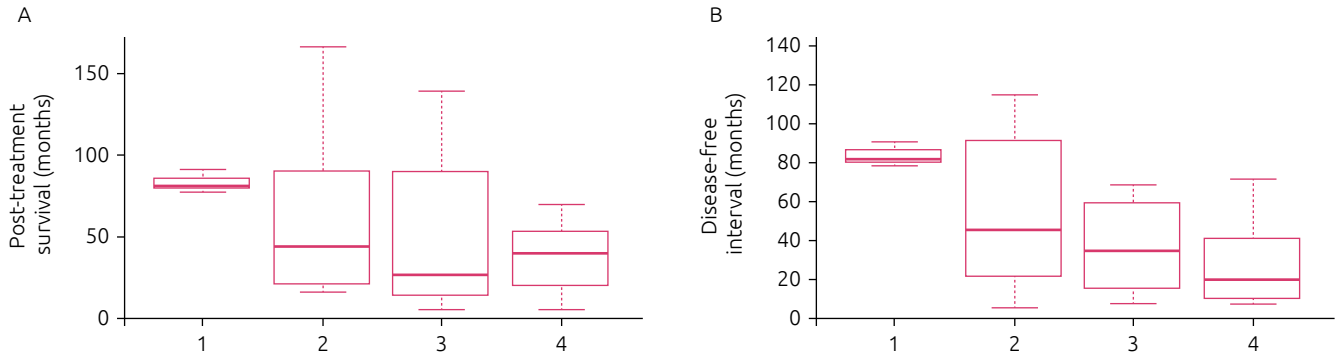
Table 4. Imaging examinations.

	BIRADS	Absolute frequency	Relative frequency (%)
US	0	2	10.5
	1	0	0
	2	0	0
	3	0	0
	4	8	42.1
	5	8	42.1
	6	0	0
	NI*	1	5.2
MMG	0	1	5.2
	1	0	0
	2	0	0
	3	1	5.2
	4	12	63.1
	5	5	26.3
	6	0	0

Data on imaging results in cases of invasive lobular carcinoma treated at HC-UFPR between 2005 and 2014; *not informed; MMG: mammography

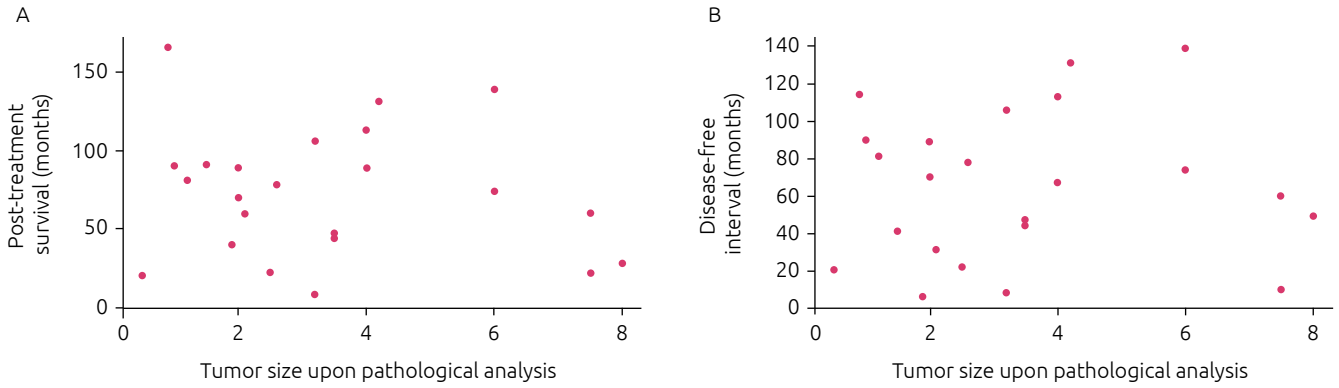
As to the molecular characteristics of tumors, the classical profile of hormone receptor positivity and HER2 negativity was predominant. The literature suggests that ILC that differ from this pattern are associated with worse prognosis, which was not evaluated in our study, since only two cases were HER2-positive[15].

The use of conservative surgery followed by adjuvant radiotherapy is a well-accepted therapeutic modality for ductal invasive breast cancers, but it is controversial when considered for ILC[24] due to the high rates of multifocality and multicentricity in ILC, which often involve compromised surgical margins requiring new therapy[20]. This can possibly explain the fact that, in our study, the surgical therapeutic modality applied in more than 70% of patients was radical mastectomy. Despite the increase



Correlation between post-treatment survival and disease-free interval versus clinical stage of patients treated for invasive lobular carcinoma at HC-UFPR between 2005 and 2014. Kruskal-Wallis test, p=0.7193 (A) and p=0.1202 (B). Comparison between stages 1 and 4 only, p=0.002 (A) and p=0.001 (B).

Graph 2. Correlation between post-treatment survival and disease-free interval. clinical stage.

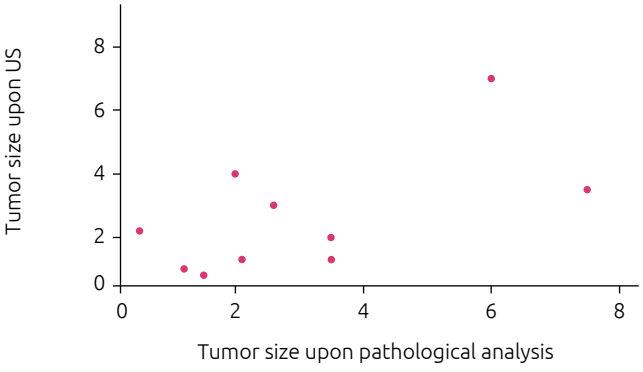


Correlation between post-treatment survival and disease-free interval versus tumor size in anatomopathological analysis of patients treated for invasive lobular carcinoma at HC-UFPR between 2005 and 2014. Spearman's correlation test, p=0.7193 (A) and p=0.7449 (B).

Graph 3. Correlation between post-treatment survival and disease-free interval versus tumor size in anatomopathological analysis.

in indications for non-radical surgical therapies, mastectomy remains the main option due to this pattern of multifocality and discreet infiltration by the breast tissue, which is difficult for the surgeon to identify[25]. Among patients assessed in our study, 21 were submitted to radiotherapy and only eight of them to conservative surgery, suggesting that some patients underwent radiotherapy for other indications such as metastatic lesions and disease recurrence.

Regarding axillary lymph node approach, our study found a predominance of axillary emptying as the initial therapy (62.9%), which can be attributed to the difficulty of detecting metastatic ILC cells in lymph nodes because they present in isolation between the lymphocyte cells of the lymph node itself, particularly in micro-metastases, hence the preference for radical surgical[26]. There is now evidence that axillary emptying is not better



Correlation between tumor size upon US and tumor size upon anatomopathological analysis of invasive lobular carcinomas treated at HC-UFPR between 2005 and 2014. Spearman's correlation test, p=0.156.

Graph 4. Correlation between tumor size upon US and tumor size in anatomopathological analysis.

than conservative sentinel lymph node treatment with regard to locoregional recurrence[27].

ILC usually has unsatisfactory response to chemotherapy and HER2-targeted therapy because of its negativity for this marker. However, hormone therapy centered on ER and PR positivity, typical of ILC, is highly indicated as adjuvant therapy capable of improving survival[28]. In our study, 71.4% of patients underwent hormone therapy, in contrast to 90% ER positive and 70% PR positive. We believe that the lack of information in medical records may be associated with the high rate of patients who did not receive this adjuvant treatment option; that is, the rest of the patients would also have received HT but data were not input in medical records. Nevertheless, previous studies have shown that patients with invasive lobular carcinoma receive less hormonal therapy than recommended[28].

The clinical staging of patients was compared to DFI and post-treatment survival. In both cases, associations were not statistically significant when all clinical stages were compared simultaneously. However, when stages I and IV were compared, there was a significant difference, which shows that both post-treatment survival and DFI were negatively impacted by advanced staging. Stages II and III not being significantly associated can be explained by the small number of samples obtained in our study and by some patients being lost to follow-up over the course of the 10 years studied.

The size of the tumor in the anatomopathological biopsy also had no significant association with DFI and post-treatment survival. Again, we attribute this the reduced number of cases in the sample and to losses of follow-up. Another similar study carried out in a Brazilian university hospital reported significant results for this association, which shows that the larger the tumor, the worse patients' survival[23].

With regard to imaging tests, only one exam was predominant (45.7%) in relation to the performance of US and mammography in combination (31.4%). The sensitivity of these two tests is controversial in the literature, varying from 57 to 89% for mammography and from 71 to 91% for US[22,29]. Because of this variability, complementing diagnosis with another imaging test in cases of greater suspicion is important to reduce errors. For an appropriate therapeutic approach to ILC, it is essential that the disease is staged correctly, and both US and mammography have shown high rates of underestimation of tumor size, as well as failures in ILC detection by mammography screening because of the similarity of tumor density with the adjacent mammary parenchyma[30]. MRI, therefore, plays a key role in ILC detection and staging definition, with a 93.3% sensitivity[29]. Unfortunately, in our series, none of the patients were referred to MRI, which exposes a deficiency of the health system in providing patients with adequate access to existing resources.

The discrepancy in size of ILC tumors in imaging and pathological analysis has been described in several studies, which suggests an underestimation of tumor size by mammography and US when compared to its actual size measured in post-surgical biopsies. Mammography has an average of 12 mm of underestimation, while in US it varies from 5.4 to 12.2 mm[29,30]. MRI, however, has a correlation index with pathology of 0.8-0.97, proving to be much more reliable for the purpose of measuring ILC tumor size[29]. In our study, we did not find a significant relationship between tumor size upon US and pathological anatomy (p=0.156). We attribute this the very small number of patients whose medical records contained this information, resulting in a very small sample for statistical analysis.

CONCLUSIONS

Our study reflects the reality of a South-Brazilian university hospital with data encompassing 10 years of medical records, which shows that the clinical-epidemiological features of patients treated for ILC at HC-UFPR are in accordance with the literature, both in incidence and in characteristics of tumors. The evaluation of ILC dimensions in imaging examinations compared to the real size of lesions identified in postoperative specimens resulted not statistically significant. We had great limitation of access to clinical data of patients due to the lack of information in medical records. This study is important because it not only depicts ILC's epidemiology in a South Brazilian hospital, but also shows the need for early diagnosis and correct use of diagnostic resources to achieve this goal.

REFERENCES

1. Instituto Nacional de Cancer José Alencar Gomes da Silva. Estimativa 2016. Brasil: Ministério da Saúde; 2016.
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC cancerbase. cancer incidence and mortality worldwide. IARC Cancer Base; 2014.
3. Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. Br J Cancer. 2005;93(9):1046-52. https://dx.doi.org/10.1038%2Fsj.bjc.6602787
4. Dossus L, Benusiglio PR. Lobular breast cancer: incidence and genetic and non-genetic risk factors. Breast Cancer Res. 2015;17:37. https://doi.org/10.1186/s13058-015-0546-7
5. Eheman CR, Shaw KM, Ryerson AB, Miller JW, Ajani UA, White MC. The changing incidence of in situ and invasive ductal and lobular breast carcinomas: United States, 1999-2004. Cancer Epidemiol Biomarkers Prev. 2009;18(6):1763-9. https://doi.org/10.1158/1055-9965.EPI-08-1082

6. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. J Am Med Assoc. 2012;288(3):321-33.
7. Wachtel MS, Yang S, Dissanaike S, Margenthaler JA. Hormone replacement therapy, likely neither angel nor demon. PLoS One. 2015;10(9):e0138556. https://doi.org/10.1371/journal.pone.0138556
8. Christgen M, Steinemann D, Kühnle E, Länger F, Gluz O, Harbeck N, et al. Lobular breast cancer: Clinical, molecular and morphological characteristics. Pathol Res Pract. 2016;212(7):583-97. https://doi.org/10.1016/j.prp.2016.05.002
9. Allen-Brady K, Camp NJ, Ward JH, Cannon-Albright LA. Lobular breast cancer: Excess familiality observed in the Utah Population Database. Int J Cancer. 2005;117(4):655-61. https://doi.org/10.1002/ijc.21236
10. Li CI, Daling JR, Haugen KL, Tang MTC, Porter PL, Malone KE. Use of menopausal hormone therapy and risk of ductal and lobular breast cancer among women 55-74 years of age. Breast Cancer Res Treat. 2014;145(2):481-9. https://doi.org/10.1007/s10549-014-2960-4
11. Newcomb PA, Trentham-Dietz A, Hampton JM, Egan KM, Titus-Ernstoff L, Warren Andersen S, et al. Late age at first full term birth is strongly associated with lobular breast cancer. Cancer. 2011;117(9):1946-56. https://dx.doi.org/10.1002%2Fcncr.25728
12. Li CI, Malone KE, Porter PL, Weiss NS, Tang MTC, Daling JR. Reproductive and anthropometric factors in relation to the risk of lobular and ductal breast carcinoma among women 65-79 years of age. Int J Cancer. 2003;107(4):647-51. https://doi.org/10.1002/ijc.11465
13. Sharma SDJ, Barry M, O'Reilly EA, Kell MR. Surgical management of lobular carcinoma from a national screening program: a retrospective analysis. Eur J Surg Oncol. 2015;41(1):79-85. https://doi.org/10.1016/j.ejso.2014.09.004
14. Lee J-H, Park S, Park HS, Park B-W. Clinicopathological features of infiltrating lobular carcinomas comparing with infiltrating ductal carcinomas: a case control study. World J Surg Oncol. 2010;8:34. https://doi.org/10.1186/1477-7819-8-34
15. 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. https://dx.doi.org/10.1186%2Fbcr767
16. Sastre-Garau X, Jouve M, Asselain B, Vincent-Salomon A, Beuzeboc P, Dorval T, et al. Infiltrating lobular carcinoma of the breast: Clinicopathologic analysis of 975 cases with reference to data on conservative therapy and metastatic patterns. Cancer. 1996;77(1):113-20. https://doi.org/10.1002/(SICI)1097-0142(19960101)77:1%3C113::AID-CNCR19%3E3.0.CO;2-8
17. Sinclair K, Sakellariou S, Dawson N, Litherland J. Does preoperative breast MRI significantly impact on initial surgical procedure and re-operation rates in patients with screen-detected invasive lobular carcinoma? Clin Radiol. 2016;71(6):543-50. https://doi.org/10.1016/j.crad.2016.03.011
18. Smith DB, Howell A, Wagstaff J. Infiltrating lobular carcinoma of the breast: Response to endocrine therapy and survival. Eur J Cancer Clin Oncol. 1987;23(7):979-82.
19. Dutra MC, Rezende MA, de Andrade VP, Soares FA, Ribeiro MV, de Paula EC, et al. Imunofenótipo e evolução de câncer de mama: comparação entre mulheres muito jovens e mulheres na pós-menopausa. Rev Bras Ginecol Obs. 2009;31(2):54-60. http://dx.doi.org/10.1590/S0100-72032009000200002
20. Biglia N, Mariani L, Sgro L, Mininanni P, Moggio G, Sismondi P. Increased incidence of lobular breast cancer in women treated with hormone replacement therapy: implications for diagnosis, surgical and medical treatment. Endocr Relat Cancer. 2007;14(3):549-67. https://doi.org/10.1677/ERC-06-0060
21. Zhu MZ, Yu XF, He XM, Feng WL, Fan JH, Li J, et al. Clinicopathological features of invasive lobular carcinoma of the breast: a nationwide multicenter study in China. J Cancer Res Ther. 2015;11(Supl. 1):C89-94. https://doi.org/10.4103/0973-1482.163851
22. Winchester DJ, Chang HR, Graves TA, Menck HR, Bland KI, Winchester DP. A comparative analysis of lobular and ductal carcinoma of the breast: presentation, treatment, and outcomes. J Am Coll Surg. 1998;186(4):416-22.
23. Gomes, DS. Aspectos clínicos, anátomo-patológicos e evolutivos de uma série de lesões lobulares da mama tratadas em uma mesma instituição [dissertation]. Belo Horizonte: Federal University of Minas Gerais. Medicine School; 2010;
24. Peiro G, Bornstein BA, Connolly JL, Gelman R, Hetelekidis S, Nixon AJ, et al. The influence of infiltrating lobular carcinoma on the outcome of patients treated with breast-conserving surgery and radiation therapy. Breast Cancer Res Treat. 2000;59(1):49-54.
25. Dillon MF, Hill ADK, Fleming FJ, O'Doherty A, Quinn CM, McDermott EW, et al. Identifying patients at risk of compromised margins following breast conservation for lobular carcinoma. Am J Surg. 2006;191(2):201-5. https://doi.org/10.1016/j.amjsurg.2005.03.041
26. Salles MDA, Cúrcio VS, Perez AA, Gomes DS, Gobbi H. Contribuição da imuno-histoquímica na avaliação de fatores prognósticos e preditivos do câncer de mama e no diagnóstico de lesões mamárias. J Bras Patol e Med Lab. 2009;45(3):213-22. http://dx.doi.org/10.1590/S1676-24442009000300006
27. Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, et al. Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases. Ann Surg. 2016;264(3):413-20. https://doi.org/10.1097/SLA.0000000000001863
28. Rakha EA, El-Sayed ME, Powe DG, Green AR, Habashy H, Grainge MJ, et al. Invasive lobular carcinoma of the breast: response to hormonal therapy and outcomes. Eur J Cancer. 2008;44(1):73-83. https://doi.org/10.1016/j.ejca.2007.10.009
29. Mann RM, Hoogeveen YL, Blickman JG, Boetes C. MRI compared to conventional diagnostic work-up in the detection and evaluation of invasive lobular carcinoma of the breast: a review of existing literature. Breast Cancer Res Treat. 2008 Jan;107(1):1-14. https://dx.doi.org/10.1007%2Fs10549-007-9528-5
30. Yeatman TJ, Cantor AB, Smith TJ, Smith SK, Reintgen DS, Miller MS, et al. Tumor biology of infiltrating lobular carcinoma. Implications for management. Ann Surg. 1995;222(4):549-61.

CASE REPORT
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PASH: STROMAL AND PSEUDOANGIOMATOUS HYPERPLASIA — SURGICAL TREATMENT USING ONCOPLASTIC TECHNIQUES — THOREK AND DERMAL FLAP

PASH: hiperplasia estromal e pseudoangiomatosa — tratamento utilizando técnicas oncopásticas — Thorek e dermal flap

Ana Carolina Guglielmelli Mendonça[1]*, Raffaela Levy de Andrade[2], Douglas de Miranda Pires[3]

ABSTRACT

Pseudoangiomatous stromal hyperplasia (PASH) is a benign and infrequent mammary pathology, characterized by abnormal proliferation of stromal cells forming a complex network of channels interconnected by vascular spaces, delineated by fusiform cells, originating from myofibroblastic cells. It is commonly found in breast biopsies as an incidental finding and, more rarely, it can form a nodular, tumor-like mass or exhibit a pattern of diffuse involvement of the breast parenchyma. It affects women aged between 18 and 45 years old and is related to hormonal stimulation. In most cases, PASH shows slow growth. The treatment recommended by most authors is a broad excision of the lesion, with free margins to avoid local recurrences. Surgical resection combined with breast reconstruction techniques allows the incorporation of concepts and techniques that respect aesthetics and improve women's quality of life. This study aimed to report the case of a 40-year-old patient with multiple bilateral breast nodules, associated with ptotic hypertrophic mastopathy, treated by adenectomy and immediate reconstruction with mammary prosthesis using Thorek's technique. The patient presented a good postoperative evolution, with excellent cosmetic results and no evidence of disease after 19 months of diagnosis.

KEYWORDS: Hyperplasia; neoplasms; breast; reconstructive surgical procedures.

RESUMO

A hiperplasia estromal pseudoangiomatosa (pseudoangiomatous stromal hyperplasia — PASH) é uma patologia mamária benigna e pouco frequente, caracterizada por proliferação anormal de células estromais que formam uma rede complexa de canais interligados por espaços vasculares, delineados por células fusiformes, oriundas de células miofibroblásticas. Comumente encontrado em biópsias de mama como achado incidental e, mais raramente, por formar uma massa nodular de aparência tumoral ou exibir um padrão de envolvimento difuso do parênquima mamário. Afeta mulheres entre as idades de 18 e 45 anos e está ligada a estímulo hormonal. Na maioria dos casos, essa patologia mostra crescimento lento. O tratamento recomendado pela maioria dos autores é uma excisão ampla da lesão, com margens livres para evitar as recidivas locais. O tratamento cirúrgico aliado à reconstrução mamária permite incorporar conceitos e técnicas que respeitam a estética e melhoram a qualidade de vida da mulher. O objetivo deste trabalho foi relatar o caso de uma paciente de 40 anos com múltiplos nódulos mamários bilaterais associados à mastopatia hipertrófica ptótica, tratada por adenectomia e reconstrução imediata com prótese mamária utilizando a técnica de Thorek. A paciente mantém-se em boa evolução pós-operatória, com excelente resultado cosmético e sem evidência de doença após 19 meses de diagnóstico.

PALAVRAS-CHAVE: Hiperplasia; neoplasia benigna; mama; procedimentos cirúrgicos reconstrutivos.

Study carried out at Santa Casa de Misericórdia de Belo Horizonte – Belo Horizonte (MG), Brazil.
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INTRODUCTION

Pseudoangiomatous stromal hyperplasia (PASH) is a benign breast disease described for the first time in 1986 by Vuitch et al.[1]. From 1986 until 2007, less than 150 reported cases of tumor-forming PASH were found[2]. In contrast, focal PASH, which does not form tumors, may be an incidental microscopic finding in up to 23% of breast biopsies[3]. Initially considered to be a variant of mammary hamartomas, this lesion is currently considered a benign proliferation of stromal myofibroblasts, expressing CD34, vimentin, actin, smooth muscle desmin and bcl-2, but not endothelial markers (CD31, Factor VIII), S100 or cytokeratin. The clinical-pathological spectrum ranges from incidental focal microscopic findings to clinically and mammographically evident mammary masses. It is histologically characterized by the interaction of angular spaces and slits aligned by thin spindle cells and surrounded by dense collagen stroma. It affects women in the age group of 18 to 45 years old[4]. Tumor-forming PASH occurs predominantly in premenopausal women and generally presents clinically as a palpable, mobile, firm, and painless breast mass. However, occasional cases have occurred in postmenopausal women, men, adolescents, and even in pediatric patients[5].

Clinical, mammographic and ultrasonographic findings are not specific and generally lead to a fibroadenoma or phyllodes tumor diagnosis[6]. Histopathogenesis is nuclear, and the literature reports that hormonal factors play a role in its development[7]. Although there are some reports of tamoxifen use, the treatment recommended by most authors is an excision of the lesion[8]. Breast reconstruction techniques, when combined with optimal surgical resection, contribute to an integral treatment for women, with preservation of sexuality and body image, and, consequently, a less traumatic rehabilitation process, bringing physical, psychological and social benefits[9].

This study aimed to report a case of a patient with multiple bilateral solid nodules, whose histopathological diagnosis of the surgical piece was PASH, and who was surgically treated by bilateral adenectomy and immediate breast reconstruction using Thorek's technique (amputation and free grafting of the aorta-nipple complex). The patient had an excellent cosmetic result, was free of relapses until the present moment, and was treated in the Mastology Clinic of Santa Casa de Belo Horizonte.

CASE REPORT

Patient E.S.F., female, 40 years old, multiparous (G3P3A0), with a family history of a mother who died of breast cancer at 42 years of age, was referred to Santa Casa de Belo Horizonte in October 2014. She had reports of multiple bilateral breast nodules of progressive growth for 4 years, which was associated with mastalgia, hypertrophy and mammary ptosis. She denied the use of combined oral contraceptives (OCs) or hormone replacement therapy and presented a history of benign nodule excision in both breasts. Clinical examination demonstrated asymmetric, hypertrophic breasts, grade III ptosis, with multiple nodules bilaterally, dermal suffering by compression, and no lymph node enlargement (Figures 1A and 1B).

Mammography was performed on 10/24/2013, which showed dense breasts with glandular components of bilateral multinodal morphology. Ultrasonography on 08/21/2014 demonstrated multiple nodular images, distorting breast architecture with irregular contours and shapes and, finally, core biopsy with a histological diagnosis of benign, fibroepithelial lesion with focal cell proliferation. Surgical removal was indicated.

In view of the positive family history for breast carcinoma, the patient's clinical condition, the histological diagnosis and the surgical impossibility of removing only the tumors (as they fully occupied both breasts), the treatment chosen was adenectomy and immediate reconstruction with an anatomical mammary prosthesis implant, with a volume of 300 cc bilaterally. Thorek's technique (amputation and free graft of the aorta-nipple complex) was used, which is associated with the construction of the lower dermal flap.

An histopathological examination confirmed the diagnosis of PASH. The resected mammary volume was 1,502 g in the right breast and 1,377 g in the left breast (Figures 2A and 2B).

The patient had a good postoperative evolution, and the drain removed on the 6th postoperative day (POD). Sponge dressings were removed on the 11th POD (Figures 3A and 3B).

The patient evolved with depigmentation of the nipple-areola complex (NAC) (Figures 4A and 4B) and underwent surgical refinement with dermopigmentation and remodeling of the inframammary sulcus after eight months (Figures 5A and 5B).

Outpatient follow-up was maintained with excellent aesthetic results and no signs of local recurrence after 19 months.

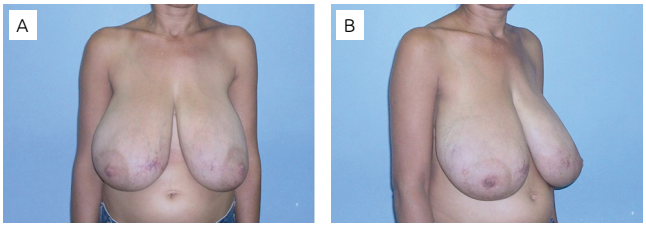

Figure 1. Preoperatively. Multiple bilateral nodules associated with hypertrophy and mammary ptosis: (A) frontal view; (B) oblique view at 45° to the right.

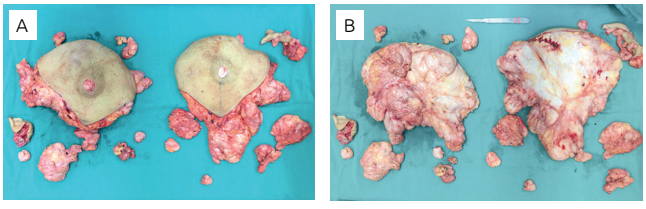

Figure 2. Perioperatively. Bilaterally resected surgical specimen: (A) anterior face; (B) posterior face.

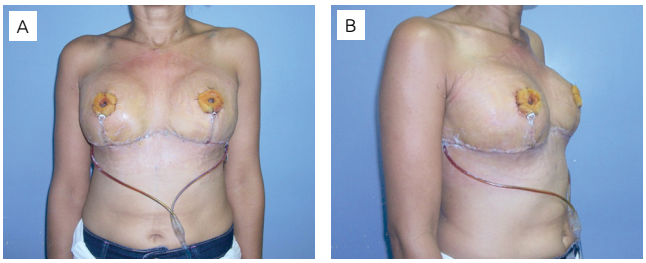

Figure 3. Fourth postoperative day: (A) frontal view; (B) oblique view at 45° to the right.

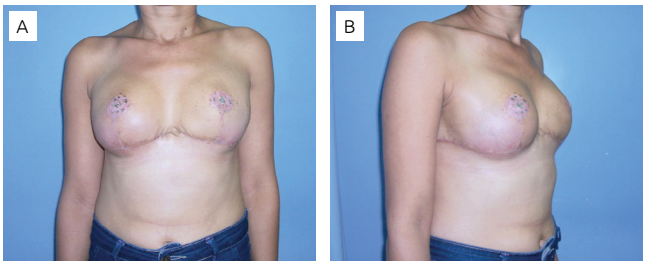

Figure 4. Two months postoperatively evolving with loss of nipple-papillary complex graft: (A) frontal view; (B) oblique view at 45° to the right.

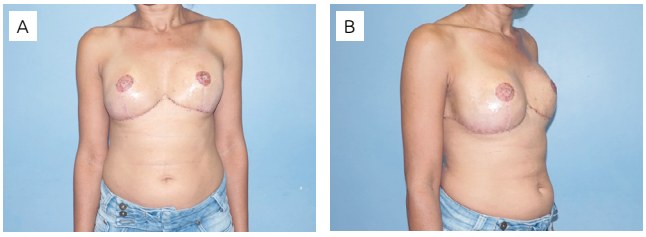

Figure 5. Postoperatively. Ten days after the nipple-papillary complex dermopigmentation and the inframammary flap repositioning: (A) frontal view; (B) oblique view at 45° to the right.

METHODOLOGY

For the case study, an analysis of the patient's chart was performed in conjunction with the gathering of their clinical history, laboratory and imaging tests, which aided in the diagnosis and follow-up of their pre, per, and postoperative evolution.

A bibliographic review was carried out through active searches in the following databases: CAPES portal, Pubmed and UpToDate.

DISCUSSION

PASH is an uncommon but benign breast lesion that affects women aged between 18 and 45 years old. It can be found incidentally on routine biopsies performed for benign or malignant breast diseases, or it present itself as clinically and mammographically evident breast masses[3,5].

Its pathogenesis is unclear, although some authors suggest that it could be an aberrant response from myofibroblasts to endogenous or exogenous hormonal stimuli. This could happen particularly from progesterone, which begins with a marked focal breast change, a physiological occurrence during the menstrual cycle[10]. It affects women primarily in the premenopausal period, but the literature also reports PASH in women in the postmenopausal period with hormone replacement therapy[11], as well as in men with gynecomastia, which also supports a hormonal-based nature of these lesions[4].

It appears clinically as a circumscribed, painless, palpable nodule, with a firm or soft consistency, and elongated or oval in shape, similar to benign solid nodules. It occasionally exhibits rapid growth and may occur bilaterally[12].

There is no specific mammographic or ultrasonographic aspect for PASH. With mammography, it is shown as a mass of well-defined or partially defined margins, and nodules with indistinct or spiculated margin have also been reported. According to ultrasonography, most of the lesions identified are solid and hypoechogenic, with some heterogeneous lesions[13,14].

PASH's characteristic histological aspect consists of empty, anastomosed fissure spaces that permeate dense and hyalinized connective tissue in the interlobular and/or intralobular stroma. These pseudovascular channels are surrounded by fusiform myofibroblastic cells[13]. This can be inferred by immunohistochemistry, which demonstrates positivity for CD34, vimentin, actin, smooth muscle desmin and bcl-24[13].

Among the differential diagnoses, the most important is low-grade angiosarcoma, which is identified by the presence of anastomosed vascular channels containing red blood cells that invade the breast tissue and are not associated with a collagen stroma[15]. The stromal cells in PASH generally have a benign nuclear appearance, in contrast to the atypical appearance of angiosarcoma.

Due to cellularity, PASH can also be confused with phyloid tumors, although they do not have the typical abnormal glandular configuration of this tumor. Finally, it is possible to mistake PASH for fibroadenoma if the pseudovascular spaces are not recognized[10].

A definitive histological diagnosis can be performed by an excisional or core needle biopsy. Although some authors recommend the excision of the lesion to evaluate the possibility of associated fibroepithelial neoplasia, when the use of a core needle identified PASH [13], Cohen et al. reports that if the imaging findings are consistent with breast PASH, confirming the diagnosis with a surgical biopsy is not required[14].

A vacuum-assisted biopsy, although not routinely applied for complete excision, can be safe and useful when a specific and precise diagnosis is necessary.

To date, there is only one reported case that suggests a malignant transformation of a PASH lesion, and only rare cases

have been reported in which this pathology was associated with malignancy[16].

The treatment recommended by most authors is extensive local excision. A recently published study has shown that non-surgical management strategies can be considered for patients who refuse surgical procedures, and these options may be acceptable especially when the lesion is small and a triple assessment has been performed to exclude a malignant disease[17]. Some reports have shown an impressive response to tamoxifen in a patient with breast enlargement, pain and breast masses[8]. However, prolonged use may not be ideal, considering the possible side effects.

A mastectomy has been reported to control multiple nodular recurrence[18,19]. The rates of PASH relapse after excision are rare and range from 15 to 22%, and the prognosis is excellent[1,18].

The above reported case of an uncommon clinical presentation shows a patient with multiple bilateral nodules with progressive growth, which associated with hypertrophic ptotic mastopathy. This caused great discomfort and patient dissatisfaction. Because the histopathological diagnosis of core biopsy was not definitive, and considering the family history of breast neoplasm and the clinical condition of the patient, surgical resection was chosen. This consisted of a bilateral adenectomy and immediate reconstruction with an anatomical prosthesis using Thorek's technique and a dermal flap technique, followed by surgical refinement with a nipple-papillary complex dermopigmentation and a repositioning of the inframammary fold eight months after the first surgery. The proposed treatment had the following objectives:

- Complete resection of lesions for a definitive diagnosis;
- Improvement in the patient's symptomatology;
- Preservation of body image with physical, psychological and social benefits.

CONCLUSION

PASH is a rare, benign mammary pathology that often presents itself as a nodular mass with progressive growth, which can cause painful symptoms and deformities in the breast. It predominantly affects premenopausal women, and its pathogenesis is related to hormonal stimulation. There is no specific clinical or radiological change, but the association of these factors is essential for its diagnosis.

Although there are reports of tamoxifen treatment, the recommended course of action is surgery, which, when associated with breast reconstruction, is an excellent option for cases of bulky masses, multiple lesions and large deformities in the breast, resulting in a significant improvement in quality of life. Most of the reports published so far refer to radiological aspects, the pathology, and a series of PASH cases. Few cases of surgical resection followed by immediate breast reconstruction have been published.

REFERENCES

1. Vuitch MF, Rosen PP, Erlandson RA. Pseudoangiomatous hyperplasia of mammary stroma. Hum Pathol. 1986;17(2):185-91.
2. Wieman SM, Landercasper J, Johnson JM, Ellis RL, Wester SM, Lambert PJ, et al. Tumoral pseudoangiomatous stromal hyperplasia of the breast. Am Surg. 2008;74:1211-4.
3. Ibrahim RE, Sciotto CG, Weidner N. Pseudoangiomatous hyperplasia of mammary stroma. Some observations regarding its clinicopathologic spectrum. Cancer. 1989;63:1154-60.
4. Milanezi MF, Saggioro FP, Zanati SG, Bazan R, Schmitt FC. Pseudoangiomatous hyperplasia of mammary stroma associated with gynaecomastia. J Clin Pathol. 1998;51:204-6.
5. Shehata BM, Fishman I, Collings MH, Wang J, Poulik JM, Ricketts RR, et al. Pseudoangiomatous stromal hyperplasia of the breast in pediatric patients: an underrecognized entity. Pediatr Dev Pathol. 2009;12:450-4. https://doi.org/10.2350/08-09-0528.1
6. Hargaden GC, Yeh ED, Georgian-Smith D, Moore RH, Rafferty EA, Halpern EF, et al. Analysis of the mammographic and sonographic features of pseudoangiomatous stromal hyperplasia. AJR Am J Roentgenol. 2008;191:359-63. https://doi.org/10.2214/AJR.07.2479
7. AbdullGaffar B. Pseudoangiomatous stromal hyperplasia of the breast. Arch Pathol Lab Med. 2009;133:1335-8. https://doi.org/10.1043/1543-2165-133.8.1335
8. Pruthi S, Reynolds C, Johnson RE, Gisvold JJ. Tamoxifen in the Management of Pseudoangiomatous Stromal Hyperplasia. Breast J. 2001;7(6):434-9.
9. Audretsch WP, Rezai M, Kolotas C, Zamboglou N, Schnabel T, Bojar H. Tumor-Specific Immediate Reconstruction in Breast Cancer Patients. Seminars Plastic Surgery. 1998;11(1):71-100. DOI: 10.1055/s-2008-1080243
10. Cyralk D, Carpenter PM. Breast imaging case of the day. Pseudoangiomatous stromal hyperplasia. RadioGraphics. 1999; 19:1086-8. https://doi.org/10.1148/radiographics.19.4.g99jl201086
11. Anderson C, Ricci A Jr., Pedersen CA, Cartun RW. Immunocytochemical analysis of estrogen and progesterone receptors in benign stromal lesions of the breast. Evidence for hormonal etiology in pseudoangiomatous hyperplasia of mammary stroma. Am J Surg Pathol. 1991;15:145-9.
12. Ryu EM, Whang IY, Chang ED. Rapidly growing bilateral pseudoangiomatous stromal hyperplasia of the breast. Korean J Radiol. 2010;11(3):355-8. DOI: 10.3348/kjr.2010.11.3.355

13. Chagas CR, Menke CH, Vieira RJS, Boff RA. Tratado de mastologia da SBM. Rio de Janeiro: Revinter; 2011. p.479-81.

14. Cohen MA, Morrison EA, Rosen PP, Dershaw DD, Liberman L, Abramson AF. Pseudoangiomatous stromal hyperplasia: mammographic, sonographic and clinical patterns. Radiology. 1996;198:117-20. https://doi.org/10.1148/radiology.198.1.8539361

15. Kopans D. Breast Imaging. Filadélfia: Lippincott-Raven Publishers; 2007.

16. Nassar H, Elieff MP, Kronz JD, Argani P. Pseudoangiomatous stromal hyperplasia (PASH) of the breast with foci of morphologic malignancy: a case of pash with malignant transformation? Int J Surg Pathol. 2010;18:564-9. https://doi.org/10.1177/1066896908320835

17. Sng KK, Tan SM, Mancer JF, Tay KH. The contrasting presentation and management of pseudoangiomatous stromal hyperplasia of the breast. Singapore Med J. 2008;49:e82-5.

18. Powell CM, Cranor ML, Rosen PP. Pseudoangiomatous stromal hyperplasia (PASH). A mammary stromal tumor with myofibroblastic differentiation. Am J Surg Pathol. 1995;19:270-7.

19. Piccoli CW, Feigi SA, Palazzo JP. Developing asymmetric breast tissue. Radiology. 1999;211:111-7. https://doi.org/10.1148/radiology.211.1.r99ap42111

CASE REPORT
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BREAST METASTASIS OF A CUTANEOUS SQUAMOUS CELL CARCINOMA: CASE REPORT

Carcinoma escamocelular metastático para mama: relato de caso

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ABSTRACT

Breast cancer is the most frequent malignant tumor in women. However, squamous cell carcinoma (SCC) of the breast is very rare. Several pathological criteria are required to establish a firm diagnosis of primary SCC of the breast: 1) the tumor origin must be independent from the overlying skin and nipple; 2) the infiltrating component of the breast cancer must be predominantly of squamous type (>90%); 3) no other invasive neoplastic elements, ductal, mesenchymal or otherwise, must be present in the tumor; 4) another site of primary SCC in the patient must have been excluded. The metastatic lesion involving the breast may occur due to a metastasis from a contralateral mammary cancer or originate in any extramammary site. Breast metastases do not normally express estrogen, progesterone receptors or Human Epidermal growth factor Receptor-type 2 (HER2) protein. Prognosis is poor and treatment is palliative, based on systemic therapy tailored to the primary cancer, sometimes completed by comfort loco-regional treatment of the breast lesion. The present study reports the case of a woman previously treated for cutaneous SCC with breast metastasis, but more studies of these rare tumors are needed to increase our knowledge and improve patients' outcomes.

KEYWORDS: Squamous cell carcinoma; Breast neoplasms; Neoplasm metastasis; Mastectomy; Pathology.

RESUMO

O câncer de mama é o tumor maligno mais frequente em mulheres, no entanto o carcinoma epidermoide primário da mama é muito raro. Vários critérios patológicos são necessários para estabelecer o diagnóstico de carcinoma de células escamosas (CEC) primário da mama: 1) a origem do tumor deve ser independente da pele sobrejacente e do mamilo; 2) o componente infiltrante deve ser predominantemente de tipo escamoso (>90%); 3) nenhum outro elemento neoplásico invasivo, como ductal ou mesenquimal, deve estar presente no tumor; 4) um sítio primário de CEC deve ter sido excluído. Já os tumores secundários na mama podem ocorrer em razão de tumores na mama contralateral ou ter origem em praticamente qualquer sítio extramamário. As metástases para mama, normalmente, não expressam receptores de estrogênio nem de progesterona ou proteína Human Epidermal growth factor Receptor-type 2 (HER2). O prognóstico, na maioria dos casos, é pobre e o tratamento paliativo, com base na terapia sistêmica adaptada ao câncer primário, às vezes completada pelo tratamento locorregional da lesão mamária. O presente trabalho relata o caso de uma mulher previamente tratada por carcinoma escamocelular de pele, evoluindo com metástase para mama, porém mais estudos sobre esses tumores raros são necessários para aumentar o conhecimento e melhorar os resultados obtidos por esses pacientes.

PALAVRAS-CHAVE: Carcinoma de células escamosas; Neoplasias da mama; Metástase neoplásica; Mastectomia; Patologia.

Study carried out at Obras Sociais Irmã Dulce, Hospital Santo Antônio – Salvador (BA) – Brazil.
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INTRODUCTION

Squamous cell carcinoma (SCC) is common in skin and organs, such as in the esophagus and anus. Primary breast SCC is very rare, representing less than 0.1% of all malignant breast neoplasms[1]. Several pathological criteria are necessary to establish the diagnosis of primary breast SCC:

- the tumor's origin must be independent from the overlying skin and from the nipple;
- the infiltrating component must be predominantly of squamous type (>90%);
- no other invasive neoplastic element, such as ductal or mesenchymal, must be present in the tumor;
- a SCC primary spot must have been excluded[2].

According to the World Health Organization (WHO) classification, pure primary breast SCC belongs to the group of metaplastic breast carcinomas[3]. It is important to distinguish this entity from skin malignancies that cover the breast or metastasis from a SCC elsewhere in the body[4].

Secondary breast tumors can occur due to tumors in the contralateral breast or originate in almost any extramammary site[5]. However, breast's metastatic involvement is also very rare, representing from 0.5 to 1.5% of all malignant breast neoplasms in clinical series and 6.6% in autopsies series[6]. The types most frequently associated with breast metastases spots are: skin (melanoma), lung, prostate, intestine (intestinal carcinoid), ovary, stomach, renal cell, thyroid and soft tissue (sarcomas)[5].

Non-melanoma skin cancer is the most common in the United States, where approximately 80% are basal cell carcinomas and 20% are SCC. However, unlike basal cell carcinomas, cutaneous squamous cell carcinomas are associated with a substantial risk of metastasis[7].

The present work reports the case of a woman previously treated for skin squamous cell carcinoma which evolved with metastasis to breast and axilla, with the objective of informing and assisting in the diagnostic evaluation of this rare disease.

CASE REPORT

60-year-old female patient, farmer, from Cruz das Almas, countryside of Bahia, referred to the mastology department of Hospital Santo Antônio, Salvador, in February 2017, with intense pain and signs of phlogosis in the right axillary region for two months, with unsuccessful antibiotic treatment.

As gynecological antecedent, she reported menarche at age 15, five pregnancies, first child at age 28, spontaneous menopause at age 45, no use of hormone replacement therapy.

As comorbidities, she presented arterial hypertension, significant smoking, type II diabetes mellitus and a moderately differentiated skin squamous cell carcinoma in anterior thoracic region, resected with safety margins and tumor thickness of 0.9 cm in June 2016, with no additional treatments.

Upon physical examination, she presented large breasts, discrete edema in the right breast's lower quadrants, significant hyperemia and hardened area in ipsilateral axillary region, with impossibility of individuation of lymph nodes upon palpation.

Bilateral digital mammography only showed bilateral benign calcifications (BI-RADS II). Breast and axilla ultrasound showed a heterogeneous area with a small amount of fluid in the right breast's lower quadrants, suggesting inflammatory process, as well as a 32.4 cm heterogeneous collection in the right axillary region (BI-RADS III) (Figure 1). Magnetic resonance imaging of breasts was not performed due to social conditions and access to the Brazilian public health system (SUS).

The patient was submitted to incisional biopsy of the hardened region in axillary extension/right axilla. While awaiting the anatomopathological result, the patient's picture evolved with a large amount of blood discharge from the operative wound, fever, tachycardia and worsen edema, requiring hospitalization for antibiotic therapy and bleeding control (Figures 2 e 3).

Pathological anatomy showed a poorly-differentiated squamous cell carcinoma in the right axillary extension of the breast, with no safety margins.

Staging examinations did not indicate pathological alterations, nor did the patient mention signs or symptoms of diseases in other organs presenting squamous epithelium such as mouth, throat, esophagus, anus or cervix.

Due to her clinical picture, the patient was submitted to modified radical mastectomy for local control of the disease. In the same period, she was evaluated by the clinical oncology staff, who agreed to perform surgical treatment before systemic therapies.

During surgery, a large-dimensioned, friable tumor was found with several areas of necrosis and adhered to the interpectoral region, limiting the access to axillary content, but all the macroscopic content of the tumor was resected.

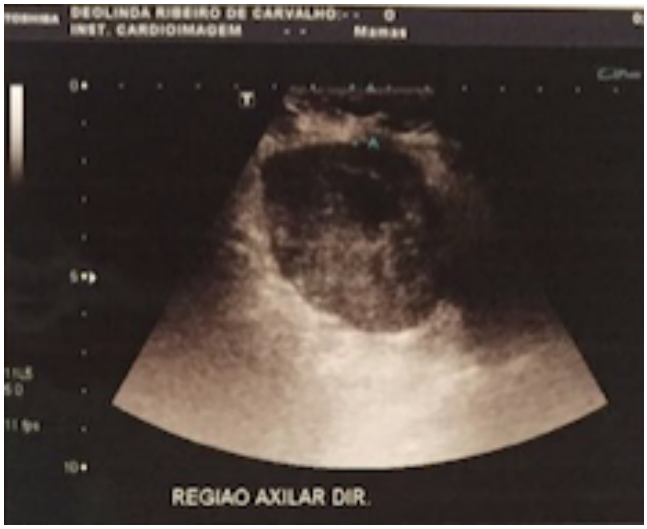

Figure 1. Heterogeneous image in the right axillary region.

Pathological anatomy of the surgical specimen was ready after 1 month and 14 days, due to SUS limitations. Characterized as a right mastectomy product weighing 3,781 g, a small poorly-differentiated breast squamous cell carcinoma (Figures 4 e 5) measuring 12.0 × 11.0 × 10.0 cm was found, with presence of neoplastic invasion in muscles and skin, no angiolymphatic invasion detected, and absence of metastasis in five of five axillary lymph nodes identified. The immunohistochemical study concluded that there was a squamous cell carcinoma with negative Human Epidermal growth factor Receptor-type 2 (HER2), negative progesterone and estrogen receptors, high Ki-67 (greater than 10%) and positive cytokeratin, of high intensity in the whole specimen (Figures 6 e 7).

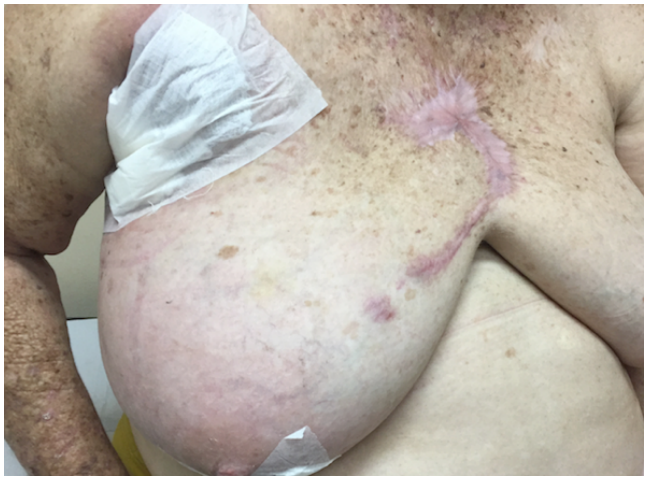

Figure 2. Image after incisional biopsy.

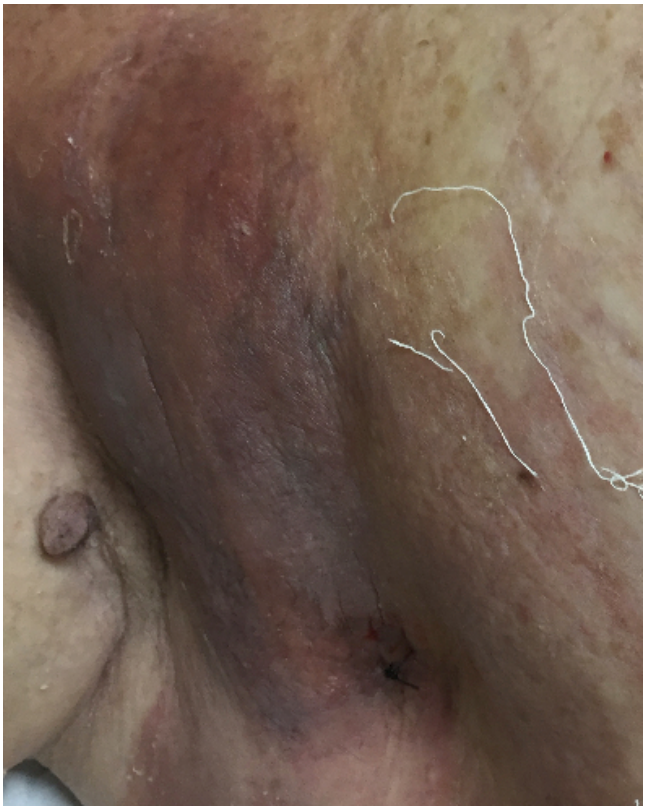

Figure 3. Right axillary region.

Few days after the surgery, the patient evolved with local pain, wound dehiscence and purulent discharge from the right axillary region. Local care and antibiotic therapy were performed, but without success in healing, making systemic therapy more difficult. The patient's clinical picture got worse, with edema, intense local pain upon oxycodone use, gabapentin and dipyrone, showing no improvement and difficulty to elevate the right upper limb, besides increase in the amount of surgical wound discharge, becoming hematic and persistent. She was referred for evaluation to a radiotherapist, who indicated anti-hemorrhagic radiation therapy with electrons with 50 Gy/20 fractions in the right axilla.

In the third session, the patient presented drowsiness, tachycardia and fever, so radiotherapy was contraindicated in the period and hospitalization was requested. Venous antibiotic therapy with ceftriaxone and clindamycin was started and bacterial cultures were collected. After three days of hospitalization,

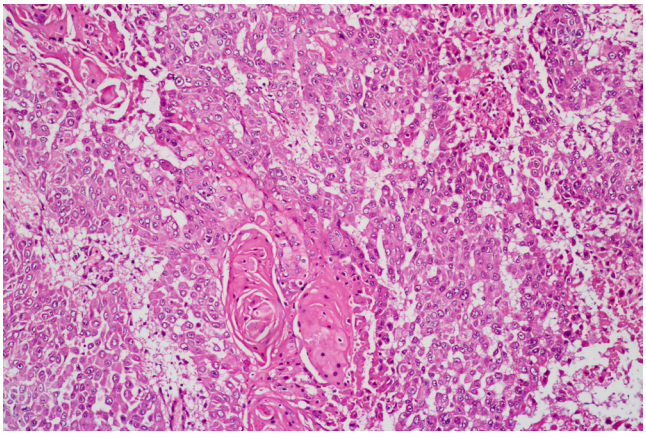

Figure 4. Infiltrative epithelial neoplasia with corneal pearl formation.

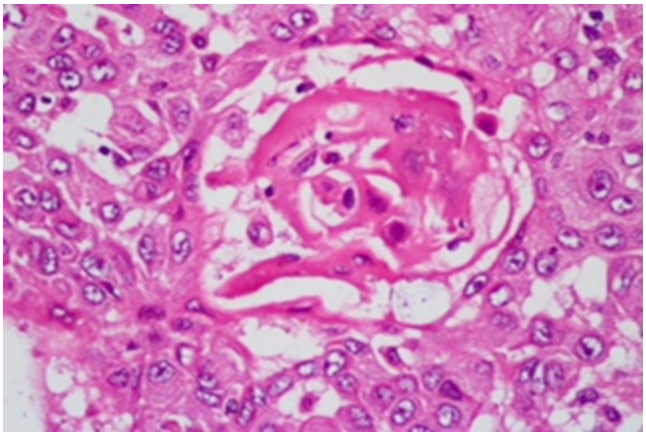

Figure 5. Atypical epithelial cell mass with central corneal pearl formation.

she presented respiratory discomfort, hypotension and level of consciousness (LOC) lowering. Thus, orotracheal intubation was performed, vasoactive drugs were introduced, antibiotics were changed to cefepime, and the patient was referred to the intensive care unit. Despite negative cultures and normal chest radiography, she underwent a new computed tomography scan of the chest, which showed nodules with soft tissue density in the middle lobe, suggesting a secondary blastomatous process without evidence of pleural effusion, and a heterogeneous mass with 9.2 cm deep necrotic areas of into the right axillary projection. At that moment, due to the clinical picture severity and disease prognosis, palliative care was introduced as jointly agreed between the relatives and the assisting medical team. After a few days, the patient evolved with cardiorespiratory arrest and obit was attested.

DISCUSSION

Breast cancer is the most frequent malignant tumor in women[8], however, primary breast squamous cell carcinoma is very rare[4]. Pure primary breast squamous cell carcinoma was first described in 1908 by Troell. It is an entity with a prevalence of less than 0.1% when compared to all malignant breast neoplasms. As per WHO classification, it belongs to the group of metaplastic breast carcinomas[3]. It is called pure SCC when malignant cells are all squamous type, without relation to the skin or any indication of primary site elsewhere in the body[9].

Due to its relative rarity, there are still no universally accepted standards for its definitive diagnosis, adequate treatment and accurate prognosis, in which causes difficulty and confusion in the clinical practice[8]. Some authors, however, have reported that pure breast SCC is a very aggressive, negative-hormone receptor tumor whose refractory treatment has poor prognosis[1].

It is important to distinguish between pure SCC and mixed tumors, as some squamous cells can be found in breast adenocarcinomas and in SCC metastases originating in other organs.[9].

The pathological anatomy in this case report, as well as the immunohistochemical study, confirmed a poorly-differentiated breast squamous cell carcinoma with no other cell types present in surgical specimen and associated with recent history of moderately differentiated squamous cell carcinoma in anterior thoracic region, even without any other distant metastases. It all led to the final diagnosis of primary skin squamous cell carcinoma with metastasis to breast and axilla.

SCC occurs more frequently in the face, hands and forearms, with actinic keratosis being the most common precursor lesion.[10]. Exposure to ultraviolet radiation is the most common cause of this cancer[7]. Smoking is also a risk factor for SCC [10], to which the patient had been exposed for a long time.

Unlike almost all basal cell carcinomas, skin squamous cell carcinomas are associated with a substantial risk of metastasis[7].

Although rare, skin SCC may migrate to regional lymph nodes and other sites such as bone, brain and lungs[10]. The main factors affecting the risk of metastasis and recurrence are tumor size and location. Large lesions (>2 cm in diameter) reappear 15% more often and metastasize 30% more often than minor lesions. Just like depth greater than 4 mm or involvement of reticular dermis, subcutaneous fat, penetration of the fascia, muscle, bone or cartilage also increase the risk of recurrence and metastasis[7].

Although there was an intense search, no reports describing metastasis of skin SCC to breast or axilla were found. In this case report, the initial lesion was extensive, occupying a large portion of the anterior thoracic region and 9 mm deep, despite free resection margins, which configures increased risk for distant metastasis.

The treatment for metastatic SCC may include systemic chemotherapy or treatment with biological response modifiers, but the efficacy of these methods for distant metastatic disease has not been established[7].

Several other sites of metastasis, besides the breast, have already been described in the literature as due to the increase in survival time of patients, resulting from the multidisciplinary treatment for primary tumor[6].

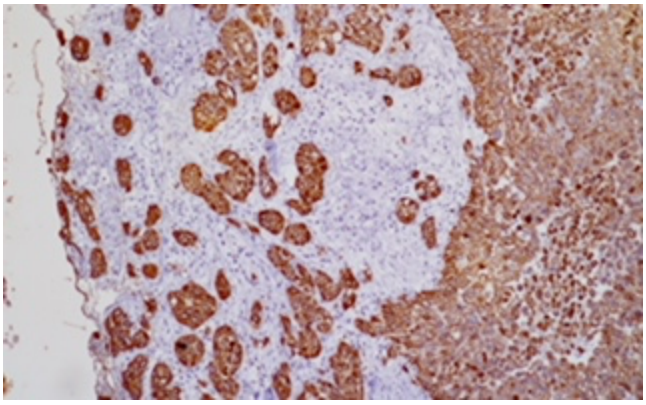

Figure 6. Diffuse positivity for high molecular weight cytokeratins (AE1 and AE3).

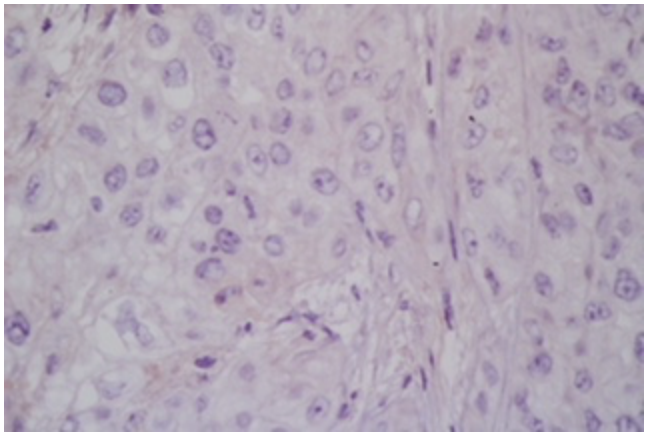

Figure 7. Negative hormone receptors.

The most common metastatic lesion affecting the breast is contralateral breast cancer metastasis.[11]. The frequency of breast metastatic tumor with extramammary malignancy, based on histological diagnosis in clinical trials, varies between 0.2 and 1.3%. In approximately 30% of patients, breast metastasis is the first sign of malignancy. In cases with history of previous malignancy, the time between initial diagnosis and breast metastasis varies from 1 month to 15 years, taking between 1 and 5 years on average.[12]. For Boff et al., the mean time to the occurrence of breast metastasis in previously treated carcinomas is two years.

The primary tumors that spread more often to the breast are, in descending order of frequency: melanoma, lymphoma, lung cancer, soft tissue sarcoma, ovarian carcinoma, gastrointestinal and genitourinary cancers[6].

Regarding diagnosis, patients typically present a palpable mass of rapid and painless growth. Some reports emphasize that masses are often superficial, but generally do not affect the skin.[12]. Mammographically, such lesions appear well defined, with non-spiculated margins, and microcalcifications are rarely present; when found, they indicate more association with metastases from ovarian tumors[5]. Ultrasound usually shows a hypoechogenic mass which is sometimes heterogeneous or poorly defined[12].

The excisional biopsy is more indicated when there is suspicion of metastatic lesion, since fine needle aspiration (FNA) has little sensitivity and specificity and core-biopsy presents low specificity for differential diagnosis with primary lesion. Regarding the immunohistochemical study, no marker is 100% sensitive or specific for any type of tumor[5]. Breast metastases do not normally express estrogen, progesterone and HER2 protein receptors[6]. The combination of cytokeratin 7 and cytokeratin 20 is useful when categorizing carcinomas[12].

Prognosis in most cases is poor, mainly because there is already a disseminated disease at the time of diagnosis, but it is also influenced by the type of primary tumor[5].

Treatment is palliative, based on systemic therapy adapted to primary cancer, sometimes complemented by locoregional treatment of mammary lesions[6]. Mastectomy is indicated only for local control of large tumors[5].

The present work depicts a case of breast and axilla metastasis of a skin SCC, up until then never described in the literature. Diagnosis was based on clinical, radiological and especially pathological arguments, associated with previous history of skin cancer. Differential diagnosis is crucial to adequate treatment provision and should be, where possible, considered for a patient with prior history of cancer.

CONCLUSION

Given the rarity of the clinical picture presented, the limited therapeutic arsenal and the reserved prognosis, its physiopathologic mechanisms should be better studied. This case report leads us to conclude that further studies are needed to increase knowledge and improve the outcomes of patients with breast metastasis from extramammary sites.

REFERENCES

1. Badge SA, Gangane NM, Shivkumar VB, Sharma SM. Primary squamous cell carcinoma of the breast. Int J Appl Basic Med Res. 2014;4(1):53-55. https://doi.org/10.4103/2229-516X.125697
2. Behranwala KA, Nasiri N, Abdullah N, Trott PA, Gui GP. Squamous cell carcinoma of the breast: clinico-pathologic implications and outcome. Eur J Surg Oncol. 2003;29:386-9. https://doi.org/10.1053/ejso.2002.1422
3. Manso P, Carnide C, Raposo J, Peralta F, Botto I. Carcinoma escamoso puro da mama. Acta Med Port. 2011;24(S3):657-60.
4. Mitra B, Pal M, Debnath S, Paul B, Saha TN, Maiti A. Primary squamous cell carcinoma of breast with ipsilateral axillary lymph node metastasis: An unusual case. Int J Surg Case Rep. 2011;2(7):194-7. https://dx.doi.org/10.1016%2Fj.ijscr.2011.06.006
5. Boff RA, de Carli AC, Brenelli H, Brenelli FP, de Carli LS, Sauer FZ, et al. Compêndio de mastologia abordagem multidisciplinar. Caxias do Sul: Lorigraf; 2015. p.457-8.
6. Sabatier R, Roussin C, Riviere JP, Jalaguier A, Jacquemier J, Bertucci F. Breast Metastasis of a Squamous Cell Carcinoma of the Uterine Cervix Mimicking Inflammatory Breast Cancer. Case Rep Oncol. 2012;5(2):464-70. https://dx.doi.org/10.1159%2F000342255
7. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med. 2001;344 (13):975-83. https://doi.org/10.1056/NEJM200103293441306
8. Chen X-L, Luo J, Xu F-L. Squamous cell carcinoma of the breast: particularity and clinical management. Int J Clin Exp Med. 2016;9(7):14167-74.
9. Bhosale SJ, Kshirsagar AY, Deshmukh SJ, Jagtap SV, Langade YB. Squamous cell carcinoma of the breast. Am J Case Rep. 2013;14:188-90. https://doi.org/10.12659/AJCR.883934
10. Broetto J, de Freitas JOG, Sperli AE, Soh SW, Richter CA, de Toni RA. Tratamento cirúrgico dos carcinomas basocelular e espinocelular: experiência dos Serviços de Cirurgia Plástica do Hospital Ipiranga. Rev Bras Cir Plást. 2012;27(4):527-30. http://dx.doi.org/10.1590/S1983-51752012000400009
11. DeLair DF, Corben AD, Catalano JP, Vallejo CE, Brogi E, Tan LK. Non-mammary metastases to the breast and axilla: a study of 85 cases. Mod Pathol. 2013;26(3):343-9. https://doi.org/10.1038/modpathol.2012.191
12. Lee AHS. The histological diagnosis of metastases to the breast from extramammary malignancies. J Clin Pathol. 2007 Dec;60(12):1333-41. https://dx.doi.org/10.1136%2Fjcp.2006.046078

CASE REPORT
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FEMALE BREAST MYOFIBROBLASTOMA: CASE REPORT

Miofibroblastoma de mama feminina: relato de caso

Claudia Teresinha Moraes Pinheiro Delgado[1]*

ABSTRACT

The myofibroblastoma of the breast is rare, being even less frequent in women. It is a benign mesenchymal tumor of uncertain etiology. The present study reports the case of a 47-year-old patient with a palpable nodule on the right breast, non-painful, having appeared approximately one year before, and with slow growth, located in an inferolateral quadrant. The biopsy pathology product describes a firm, yellowish white tissue that microscopically exhibited fusocellular proliferation without atypia, including small ductal structures with epithelial hyperplasia, suggesting immunohistochemistry which revealed expression of desmin and smooth muscle actin. Based on the morphological and anatomopathological picture, the diagnosis of breast myofibroblastoma was confirmed. Sectorectomy surgery was performed as treatment

KEYWORDS: Breast; myofibroblastoma; immunohistochemistry; diagnosis.

RESUMO

O miofibroblastoma de mama é raro, sendo menos frequente ainda em mulheres. Trata-se de um tumor mesenquimal benigno de etiologia incerta. A presente descrição relata o caso de uma paciente de 47 anos, apresentando um nódulo palpável na mama direita, não doloroso, com surgimento há aproximadamente um ano e de crescimento lento, localizado em quadrante ínfero-lateral. O anatomopatológico de biópsia produto de *core biopsy* descreve tecido branco amarelado, de consistência firme, que microscopicamente apresenta proliferação fusocelular sem atipias, incluindo pequenas estruturas ductais com hiperplasia epitelial, sugerindo imuno-histoquímica, a qual revelou expressão de desmina e actina de músculo liso. Com base no quadro morfológico e anatomopatológico, confirmou-se o diagnóstico de miofibroblastoma de mama. Foi realizada setorectomia como tratamento.

PALAVRAS-CHAVE: Mama; miofibroblastoma; imuno-histoquímica; diagnóstico.

Study carried out at the Reference Center for Child and Women's Health (CRESCEM) – Itajaí (SC), Brazil.
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INTRODUCTION

Myofibroblastoma is a benign and infrequent tumor of the breast that mainly affects men. It is a rare, fusiform cell tumor that derives from fusiform mesenchymal cells, probably originating in the fibroblasts. The case reported is of a 47-year-old patient with palpable nodulation in the right breast, located in the inferolateral quadrant, non-painful, slow-growing, with a confirmed diagnosis of myofibroblastoma.

CASE REPORT

LSC, 47 years old, female, Caucasian, I gestation, I child-birth, diabetic, with no family history of cancer, sought out ambulatory care due to a palpable nodule of slow growth in her right breast, which had appeared approximately one year before. On physical examination, the patient had large breasts and a palpable nodule of approximately 3 cm in diameter (Figure 1), of fibroelastic consistency, located in her right breast's inferolateral quadrant, with smooth and regular borders, movable and non-painful to palpation, free axillary lymph nodes and absence of papillary discharge.

Mammography, ultrasonography and core biopsy of the nodule were requested. Upon return, the mammogram presented an oval image in the right breast, with sharp edges, but a piece of the image was cut (Figure 2). Ultrasound revealed a nodular, hypoechoic image with lobulated contours, with a greater axis parallel to the cutaneous plane, without posterior acoustic event, measuring 31 × 21 × 26 mm, spaced about 57 mm from the papilla and 10 mm from the skin. According to the report, it was a solid nodule of possibly benign nature (Figure 3). Core biopsy of the nodule was performed and with the anatomopathological examination, immunohistochemistry was requested. The anatomopathological result described that, macroscopically, five filiform fragments of yellowish white tissue with firm consistency were analyzed, the largest measuring 1.3 cm and the smallest 0.7 cm. As a conclusion, fusocellular proliferation was obtained without atypia, including small ductal structures with epithelial hyperplasia. An immunohistochemical study was suggested to aid in the differential diagnosis between pseudoangiomatous stromal hyperplasia, fibromatosis, tumor phyllodes and other possibilities. The result of immunohistochemistry revealed mammary tissue with proliferation of spindle cells with eosinophilic cytoplasm and vesiculous nuclei with inconspicuous nucleoli, arranged in fascicles, interrupted by thickened collagen fibers, revealing expression of positivity for the antibodies calponin (clone Calp), desmin (clone D33) and smooth muscle actin (clone 1A4), confirming the diagnosis of myofibroblastoma. Sectorectomy was performed as treatment in the right breast, with removal of the nodulation (Figures 4 and 5). All the material was sent for anatomopathological study.

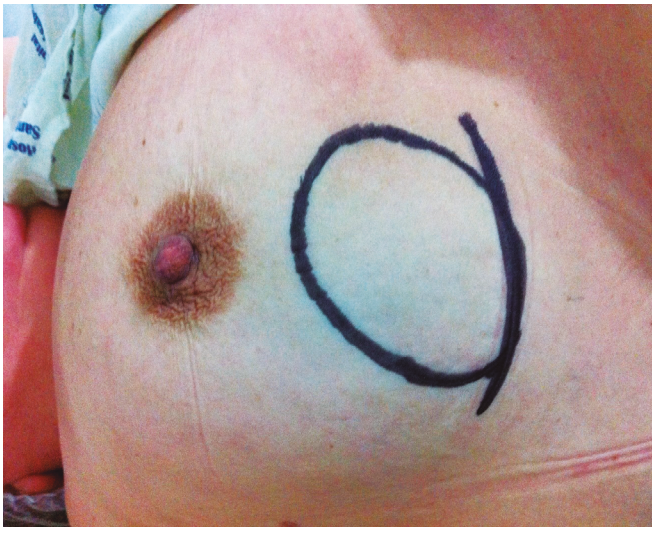

Figure 1. Location of breast nodule.

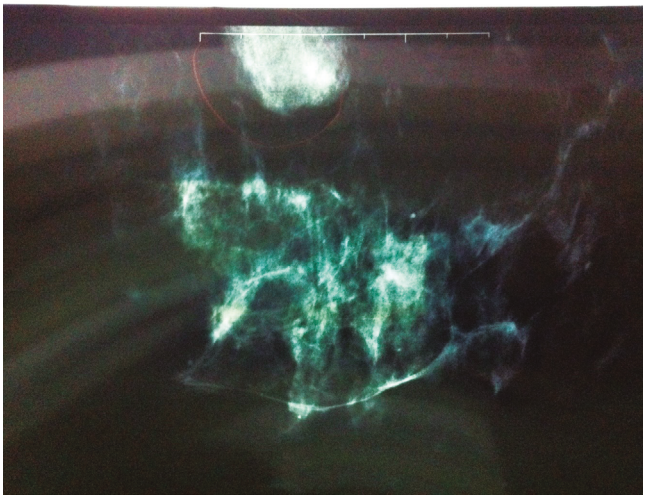

Figure 2. Nodule seen in mammographic image.

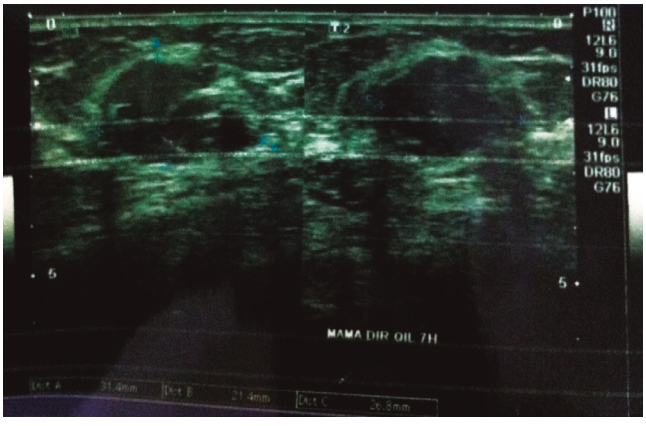

Figure 3. Ultrasound imaging.

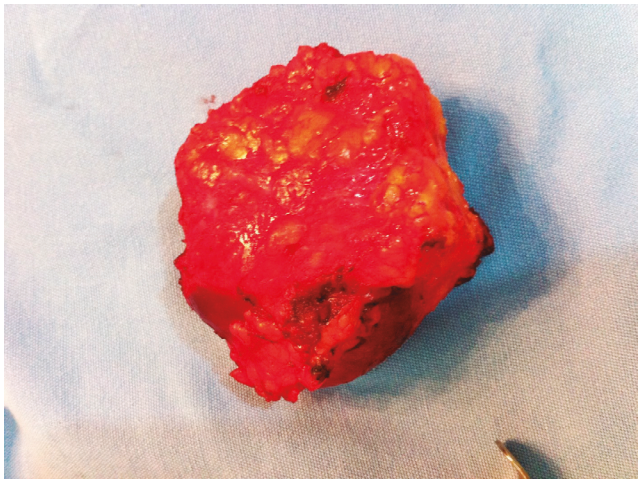

Figure 4. Closed surgical part.

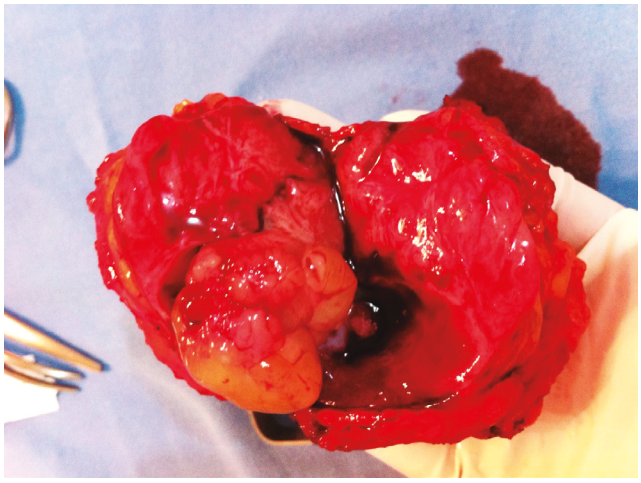

Figure 5. Open surgical part.

DISCUSSION

Myofibroblastoma is a benign and rare tumor that mainly affects male breasts[1]. The literature shows a higher frequency in men between the sixth and eighth decades of life, but some authors mention equal incidence between men and women[2]. There are approximately 80 published cases of myofibroblastoma, which was first described in 1987 by Campos et al.[3]. The tumor has mesenchymal origin and is characterized by the proliferation of fusiform cells surrounded by collagen and derived from fibroblasts. They do not metastasize and have a low rate of recurrence[2]. Immunohistochemistry reveals positivity for vimentin, actin, and desmin[4].

Macroscopically, they are well delimited tumors, firm and elastic, unencapsulated, round or oval, with sizes varying from a few millimeters to 15 cm[3]. Mammography usually reveals a single lesion, well delimited, round or discreetly lobulated[4]. Differential diagnosis should be made, among others, with gynecomastia, carcinoma, sarcoma and metastases. Ultrasound allows to rule out cystic lesions, lipomas, abscesses and hematomas[3].

Immunohistochemistry plays a fundamental role in some cases[3], such as the one reported in this study, which confirmed positivity for the antibodies calponin, desmin and actin, revealing myofibroblastoma through morphological and immunohistochemical findings.

The pathogenesis of mammary myofibroblastoma is uncertain. The high incidence in men led some authors to investigate the possible role of androgens in this tumor[2]. They concluded that the ***in situ*** detection of estrogen, progesterone and androgen receptor suggests that steroid hormones and their receptors are implicated in the pathogenesis of mammary myofibroblastoma[2]. However, we observed that, in the case described, myofibroblastoma affected a female patient and her immunohistochemistry demonstrates antibody for negative estrogen receptor (SP1).

Tumor's surgical resection is the treatment of choice, and so far there are no descriptions of local recurrences or metastases of myofibroblastoma[3].

FINAL CONSIDERATIONS

The report of this type of pathology is important due to its rarity, in general, but mainly because this is a female patient, which does not match the reality described in the literature. This case demonstrates the possibility of a differential diagnosis of benign breast tumor and the importance of requesting immunohistochemistry to define it.

REFERENCES

1. Spinetti D, Bermudez C, Betancourt L, Martínez P, Romero G, Sánchez R, et al. Miofibroblastoma de la mama feminina: reporte de un caso. Rev Venez Oncol. 2010;22(4).
2. Betancourt LIL, Rodriguez NR, Ramos JM, Avendaño GG. Miofibroblastoma mamario: incidencia, hallazgos clinico-patologicos y de imagen. Anal Radiol México. 2006;3:195-200.
3. Campos RS, Diana CF, Vilanova AG, González JM, Moratalla CN. Miofibroblastoma de mama en el varón: un desafío diagnóstico. A propósito de 2 casos. Rev Senol Patol Mamar. 2017;30:85-6. DOI: 10.1016/j.senol.2016.06.008.
4. Borobia AR, Fernández IR, Comín LM, González CZ, Sánchez EV. Tres casos de tumores mamarios infrecuentes: adenomioepitelioma, miofibroblastoma y schwannoma. Rev Senol Patol Mamar. 2001;14(4):156-60.

LETTHER TO EDITOR
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IMPACT OF MICROMETASTASIS AND ISOLATED TUMOR CELLS FOUND ON SENTINEL LYMPH NODES IN EARLY BREAST CANCER

Impacto do encontro de micrometástase e células tumorais isoladas nos linfonodos sentinela no câncer de mama precoce

Antonio Cassio Assis Pellizzon[1]*

ABSTRACT

The presence of axillary lymph node metastases is one of the most important prognostic factors in breast cancer and it is often used to guide locoregional and systemic therapy decisions. The question of whether axillary dissection (AD) can be safely omitted in patients with early breast cancer when isolated tumor cells (ITC) or micrometastasis is found in the sentinel node remains a controversial issue in the literature. On the basis of current evidence, AD could probably be safely omitted when micrometastasis or ITC are found. On making this decision, as micrometastasis and ITC are a sign of a biologically different disease, adjuvant radiotherapy and the adjuvant systemic treatment need to be considered.

KEYWORDS: Sentinel Lymph Node Biopsy; Radiotherapy; Breast Cancer; Micrometastasis.

RESUMO

A presença de metástases linfonodais axilares é um dos fatores prognósticos mais importantes no câncer de mama e é freqüentemente utilizada para guiar as decisões da necessidade de terapias locorregional e/ou sistêmica adicionais. A questão se a dissecção axilar (AD) pode ser omitida com segurança em pacientes com câncer de mama precoce, quando células tumorais isoladas ou micrometástases são encontradas no linfonodo sentinela, permanece um assunto controverso na literatura. Com base nas evidências atuais, a AD poderia ser omitida quando micrometástases ou CTI são encontradas. Ao tomar essa decisão, deve-se levar em conta que a presença de micrometástases e CTI são sinais de uma doença biologicamente diferente, em que a radioterapia adjuvante e o tratamento sistêmico adjuvante precisam ser considerados.

PALAVRAS-CHAVE: Biópsia de Linfonodo Sentinela; Radioterapia; Câncer de Mama; Micrometástase.

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Numerous studies have shown that the status of the sentinel lymph node is an accurate predictor of the status of axillary nodes in breast cancer, thus avoiding total axillary dissection (AD) in selected cases. For patients who had surgical intervention in the axilla, long-term sequels may include sensory neuropathy, lymphedema, and/or motor neuropathy.

The first randomized trial to validate sentinel-node biopsy (SNB) in breast cancer was published in 2003. The sample consisted of 516 patients with primary breast cancer, whose tumor was less than or equal to 2 cm in diameter assigned to either SNB and AD or to SNB followed by AD only if the sentinel lymph node contained metastasis. As a result, they noted that the sentinel lymph node was positive in 83 of the 257 patients in the AD group (32.3%), and in 92 of the 259 patients in the SNB group (35.5%). It was also observed that the overall accuracy of the sentinel-node status in the AD group was 96.9%, the sensitivity 91.2%, and the specificity 100%, concluding that SNB is a safe and accurate method of screening the axillary nodes for metastasis in women with small breast cancer[1]. SNB became an integral part of the conservative treatment of breast cancer since it allowed for the avoidance of AD in a large proportion of patients with early breast cancer, while still providing information to guide adjuvant treatment. More recent data also confirmed the value of SNB. The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC)[2] and the NSABP B32[3] recruited 954 and 5,611 women, respectively, and identified the value of SNB procedures in invasive breast cancer patients with clinically negative axilla.

There are three options if a tumor sentinel lymph node is positive:

- proceed to AD;
- irradiate the axilla;
- observe.

The standard approach for these patients has been to carry out an AD, once it is supposed to be a therapeutic treatment and can provide the additional information needed to direct adjuvant treatments.

The advantages of SNB include an enhanced pathological examination of a small number of sentinel lymph nodes. In the era of SNB, the sentinel lymph node is serial sectioned and all sections examined, conversely to the era before SNB, where about three sections per axillary lymph node were typically examined[4]. When sentinel lymph nodes are sliced at 2.0 mm intervals and totally embedded, the probability of identifying all metastases with more than 2.0 mm is high. Staging guidelines have established a lower limit for micrometastases and defined metastases no larger than 0.2 mm as isolated tumor cells (ITC)[5]. An increased number of micrometastases or ITC have been described and the question of whether AD can be safely omitted in patients with early breast cancer when micrometastases or ITC are found in the sentinel lymph node remains a controversial issue[6].

At the same time, however, SNB raises two new concerns: does the involvement by micrometastasis or ITC significantly impact on survival and should patients with such minimal involvement undergo further AD? The consequences of increased detection of micrometastasis has not been fully explored.

Micrometastatic disease from breast cancer is a major concern both for clinicians and pathologists. They can be defined as potentially invasive microfoci of tumoral cancer cells. Micrometastatic disease is mainly looked for in bone marrow and lymph nodes specimens. Their diagnosis is currently easier due to immunohistochemistry[7].

The further management of micrometastatic disease in the era of SNB has been evolving. Gradually, guidelines are shifting away from clearing the axilla if micrometastases are found during sentinel lymph node biopsy[8,9].

The MIRROR study showed that patients with micrometastasis and ITC who didn't receive systemic treatment had a higher event rate than those who did[10]. A recent study by Youssef et al., despite the limitations of a retrospective study and small number of patients (n=95), found a 7.01% difference in overall survival (OS) favoring the AD over the SNB group (p=0.004)[11].

In contrast, prospective early outcome data in SNB suggest no adverse outcome for patients with metastases no larger than 2.0 mm, a finding aligned with the current definition of micrometastasis[5]. The IBCSG 23–01 was a two-group, multicentered, randomized, non-inferiority, phase 3 trial comparing no-AD with AD in patients with breast cancer and micrometastases in the sentinel lymph node. Patients were recruited from 27 institutions and considered eligible if they had clinically non-palpable axillary lymph node(s), a primary tumor of 5 cm or less and who, after SNB, had one or more micrometastatic (≤mm) sentinel lymph node(s) with no extracapsular extension. Between April, 2001 and February, 2010, 465 patients were randomly assigned to AD and 469 to no-AD. The results showed no difference of outcomes in terms of disease free survival or overall survival when the axillary treatment was omitted for micrometastasis in SNB[12].

On the basis of current evidence, AD could probably be safely omitted after SNB when micrometastases or ITC are found, given the higher rate of lymphoedema and the little staging information it further adds[13]. On making this decision, as micrometastases and ITC found in the SNB are a sign of a biologically different disease, the field of adjuvant radiotherapy and the adjuvant systemic treatment need to be considered. The results of prospective large trials on going, among them the *Sentinelle Envahi et Randomisation du Curage* (SERC) study[14], may provide further evidence on this matter.

REFERENCES

1. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med. 2003;349:546-53. https://doi.org/10.1056/NEJMoa012782
2. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst. 2006 May 3;98(9):599-609. https://doi.org/10.1093/jnci/djj158
3. 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. National Surgical Adjuvant Breast and Bowel Project) B32. Lancet Oncol. 2010 Oct;11(10):927-33. https://doi.org/10.1016/S1470-2045(10)70207-2
4. Viale G, Maiorano E, Mazzarol G, Zurrida S, Galimberti V, Luini A, et al. Histologic detection and clinical implications of micrometastases in axillary sentinel lymph nodes for patients with breast carcinoma. Cancer. 2001;92:1378-84.
5. Weaver DL. Sentinel lymph nodes and breast carcinoma: which micrometastases are clinically significant? Am J Surg Pathol. 2003 Jun;27(6):842-5.
6. Bundred NJ, Barnes NL, Rutgers E, Donker M. Is axillary lymph node clearance required in node-positive breast cancer? Nat Rev Clin Oncol. 2015 Jan;12(1):55-61. https://doi.org/10.1038/nrclinonc.2014.188
7. Nahon S, Brewer Y, Kirscher S, Chauvet B, Berger C, Serin D. Axillary lymph node and bone marrow micrometastases of breast cancer. Bull Cancer. 2001 Nov;88(11):1095-104.
8. Giuliano AE, Morrow M, Duggal S, Julian TB. Should ACOSOG Z0011 change practice with respect to axillary lymph node dissection for a positive sentinel lymph node biopsy in breast cancer? Clin Exp Metastasis. 2012 Oct;29(7):687-92. https://doi.org/10.1007/s10585-012-9515-z
9. Lyman GH, Giuliano AE, Somerfield MR, Benson AB 3rd, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol. 2005 Oct 20;23(30):7703-20. https://doi.org/10.1200/JCO.2005.08.001
10. de Boer M, van Deurzen CH, van Dijck JA, Borm GF, van Diest PJ, Adang EM, et al. Micrometastases or isolated tumor cells and the outcome of breast cancer. N Engl J Med. 2009 Aug 13;361(7):653-63. https://doi.org/10.1056/NEJMoa0904832
11. Youssef MM, Cameron D, Olsen S, Ferguson D. Does axillary lymph node dissection impact survival in patients with breast cancer and isolated tumour cells or micrometastasis in sentinel node? Eur J Cancer. 2017 Apr;75:167-8. https://doi.org/10.1016/j.ejca.2017.01.016
12. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4):297-305. https://doi.org/10.1016/S1470-2045(13)70035-4
13. Galimberti V, Chifu C, Rodriguez Perez S, Veronesi P, Intra M, Botteri E, et al. Positive axillary sentinel lymph node: is axillary dissection always necessary? Breast. 2011 Oct;20(Suppl. 3):S96-8. https://doi.org/10.1016/S0960-9776(11)70303-4
14. Houvenaeghel G, Resbeut M, Boher JM. Sentinel node invasion: is it necessary to perform axillary lymph node dissection? Randomized trial SERC. Bull Cancer. 2014;101(4):358-63. https://doi.org/10.1684/bdc.2014.1916

REVIEW ARTICLE
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NIPPLE SPARING MASTECTOMY: A LITERATURE REVIEW

Mastectomia poupadora do complexo areolo-papilar: uma revisão da literatura

Douglas de Miranda Pires[1], Eduardo José Souza da Fonseca[1]*, Carolina Nazareth Valadares[2], Raffaela Levy Andrade[1], Mariana dos Santos Nascimento[1], Anna Maria Fonseca Albuquerque[3]

ABSTRACT

Introduction: The treatment of carcinoma in the early stages of breast cancer has achieved significant evolution in recent years. These developments culminated in the replacement of conventional mastectomy by more conservative techniques, such as nipple sparing mastectomy (NSM). This technique has been gaining space due to the fact that, in skin sparing mastectomy, the removal of the areola-papillary complex substantially compromises aesthetic results; despite recent and varied techniques of reconstructing of this complex, the dissatisfaction observed is of about 36% of the patients undergoing this procedure. **Objective:** Reviewing the literature about nipple sparing mastectomy of the areola-papillary complex, its oncological safety, selection criteria, surgical techniques and complications. **Discussion:** Oncologic safety is acceptable as long as matters such as selection criteria, low rate of complications and varied and feasible surgical techniques are in compliance. **Conclusion:** We found a current trend, in various institutions, to the standardization of the nipple sparing mastectomy for the treatment of early breast cancer cases. In order to achieve great results with this technique we need a multidisciplinary action between the breast surgeon, the clinical oncologist and the radiation therapy specialist. This technique shows excellent oncologic safety and low rates of complications when careful patient selection is associated with a surgeon's expertise. However, larger and longer follow-up series of patients undergoing NSM are still required.

KEYWORDS: Breast cancer; subcutaneous mastectomy; breast reconstruction.

RESUMO

Introdução: O tratamento do carcinoma nos estágios iniciais do câncer de mama tem alcançado evolução significativa nos últimos anos. Essa evolução culminou com a substituição da mastectomia convencional por técnicas mais conservadoras, como a mastectomia poupadora do complexo aréolo-papilar (MPCAP). Essa técnica vem ganhando espaço em virtude da constatação de que, na mastectomia poupadora de pele, a retirada do complexo aréolo-papilar (CAP) prejudica substancialmente os resultados estéticos e de que, apesar das recentes e variadas técnicas de reconstrução do complexo, o grau de insatisfação obtido é de cerca de 36% das pacientes submetidas a esse procedimento. **Objetivo:** Revisar a literatura a respeito da mastectomia poupadora do complexo aréolo-papilar, sua segurança oncológica, critérios de seleção, técnicas cirúrgicas e complicações. **Discussão:** Observou-se segurança oncológica aceitável desde que sejam respeitados os critérios de seleção, o baixo índice de complicações e as técnicas cirúrgicas variadas e factíveis. **Conclusão:** encontramos uma tendência atual, em várias instituições, de padronização da mastectomia poupadora do complexo aréolo-papilar para o tratamento dos casos iniciais do câncer de mama. Para que se alcance um resultado ótimo com essa técnica, é necessária uma ação multidisciplinar entre o cirurgião da mama, o oncologista clínico e o radioterapeuta. Essa técnica apresenta excelente segurança oncológica e baixas taxas de complicações quando uma criteriosa seleção dos pacientes, juntamente com a expertise do cirurgião, está associada. Entretanto, séries maiores e seguimento mais longo dos pacientes submetidos à MPCAP ainda se fazem necessários.

PALAVRAS-CHAVE: Câncer de mama; mastectomia subcutânea; mamoplastia.

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INTRODUCTION

The treatment of carcinoma in early stages of breast cancer have significantly evolved over the past few years. This improvement was initiated with the implementation of skin sparing mastectomy (SSM), which granted considerable aesthetic results to reconstructive breast surgery[1].

Following this continuous replacement of conventional mastectomy techniques by more conservative ones, the nipple sparing mastectomy (NSM) was added to the arsenal of breast surgery, whose concept would be to extensively preserve the skin of the breast, including the areola-papillary complex (APC). This technique has gained space due to the fact that, in SSM, removing the areola-papillary complex substantially compromises the desired aesthetic results.

Despite recent and varied APC reconstruction techniques, either by local patching, dermopigmentation and/or skin or contralateral nipple donor grafts, various procedures are needed in order to achieve an acceptable aesthetic result[2,3]. Jabor et al.[4] reported dissatisfaction of 36% of the patients submitted to APC. It should be noted that "The APC grants personality to the breast".

The first NSM ever described was carried out in 1960 by Freeman, who used this technique to extensive benign pathologies[5,6]. However, only in the last few years has there been grater experience with NSM, due to its being indicated in the prophylaxis of breast cancer and the surgical treatment of initial cases of this pathology[7-19]. Despite some controversies regarding the risk of local recurrence, based on APC oncological involvement rates of about 58%[20] and the fact that the follow-up is too short in most clinical series, NSM has been considered safe for candidates to undergo conservative breast surgery. Currently, there is still no consensus on which patients would be selected for this technique; however, some parameters are suggested: tumor size less than 3 cm, tumor at least 2 cm away from the APC, tumors not located in the central region of the breast, absence of cutaneous involvement and clinically negative axilla[4,19-23].

This study was developed for a systematic review of the literature, aiming to evaluate: incision choice, oncologic safety, patient selection criteria, main complications and most used reconstruction techniques.

METHOD

A research was carried out in the main databases, Pubmed and Medline, as of March 2016. The terms used were: nipple sparing mastectomy, total skin sparing mastectomy, and subcutaneous mastectomy. The studies were selected based on the relevance and importance of the institutions where they were performed, as well as of the journals they were published in.

DISCUSSION

Incision choice: a wide variety of incisions has been described for NSM[5,6,8-10,24-29]. Endara et al.[30], evaluating 48 studies on NSM, observed that the radial incision is the most used one — in about 46% of the NSM —, followed by periareolar incisions (27%), in inframammary sulcus (20%), wise pattern (4%) and transareolar (percentage not available) (Figure 1 and Table 1).

Radial incision, which allows a technically safe and feasible mastectomy, in addition to being an excellent approach to

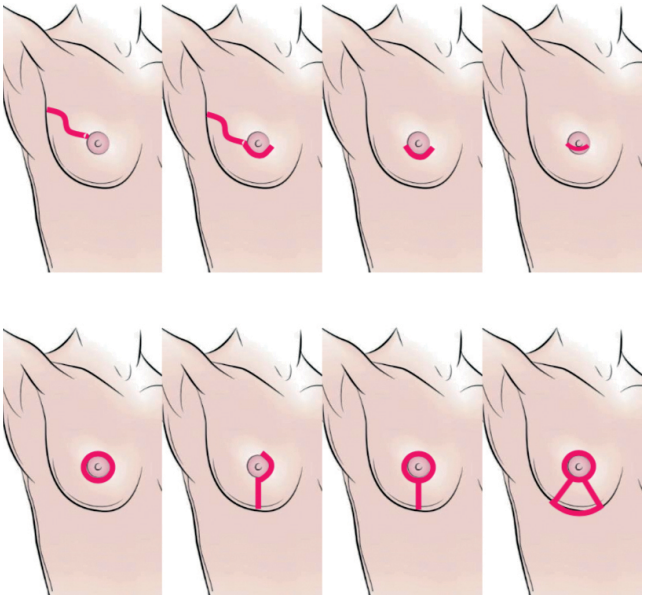

Figure 1. Types of incisions[12].

Table 1. Type of incision and main advantages, disadvantages, areola-papillary complex (APC) necrosis rate and percentage of cases performed.

Type of incision	Advantages	Disadvantages	APC necrosis	Performed in
Radial	Safe technique. Excellent surgical access to the axilla.	Scar in an aesthetically unfavorable place.	8%	46% of the cases.
Periareolar	Discreet scar, aesthetic result.	Technical difficulty, more indicated in small breasts.	18%	27% of the cases.
Inframammary sulcus	Allows placement of prosthesis of any size.	Difficult access to the upper pole of the breast and axilla.	9%	20% of the cases.
Wise pattern	Reduction of cutaneous envelope and dead space. Extensive surgical access.	Exposure of the prosthesis in case of necrosis and dehiscence.	Data not available.	4% of the cases.
Transareolar	Data not available.	High rates of APC necrosis.	82%	Data not available.

axillary extensions and content[16,31], presents APC complication rate of around 8%[32] (Table 1). One of the cons would be the resulting scar in an aesthetically debatable position[33].

The periareolar incision results in the best aesthetics, achieved by practically rendering the scar imperceptible over time. A negative aspect is its technical difficulty in most patients, being more often indicated in small breasts, with sufficient areolar diameter to allow satisfactory surgical access[33]. APC necrosis rates are observed around 18% (Table 1).

The incision in the inframammary sulcus ranks third among the most performed ones — approximately 20%[11] (Table 1). It is feasible mainly in small breasts and allows for the placement of prosthesis of any size. It presents technical difficulty both in accessing the upper pole of the breast and also the axillary tail. In some occasions, the lateral extensions of the incision or a second incision in the axillary region is necessary to remove the sentinel lymph node. It presents APC necrosis in approximately 9% of the NSM.

The wise pattern mastopexy incision is chosen in about 4% of NSMs (Table 1). It is mainly indicated for bulky breasts, with moderate to severe ptosis. Its main advantages include reduction of the cutaneous envelope and the resulting dead space between the prosthesis and the skin. It also provides a wide surgical field with satisfactory access to all quadrants of the breast and armpit. Its main disadvantage is the possibility of necrosis and/or dehiscence of operative wounds exposing the prosthesis. In order to try and minimize this complication, the inferior pole of the decorticated breast has been used as a protection for scars. Another option would be the use of an acellular dermal matrix (ADM).

The transareolar incision is considered the riskiest one due to its APC necrosis rates in about 82% of surgeries (Table 1).

Oncologic safety and patient selection criteria: concerns regarding oncologic safety stems from concept that the ducts adjacent to the tumor may contain tumor cells, which would increase the rates of local recurrence[34,35]. The mean incidence of occult tumoral involvement of APC is estimated at 11.5%, ranging from 0 to 53%[36-38]. Most studies state that NSM is safe for patients with small, non-central tumors, without multicentricity and in women undergoing risk-reducing surgeries[19].

NSM is indicated for patients with breast cancer in initial clinical stages, without cutaneous involvement and/or inflammatory carcinoma[6]. The main inclusion criteria are based on: distance between the tumor and the APC of more than 2 cm, tumors smaller than 3 cm, and lack of APC involvement[19].

Laronga et al.[39] found a higher rate of tumoral involvement of APC in patients with central (35%) and multicentric (53%) tumors. As oppose to that, a percentage of 2% of APC involvement was observed in patients with negative axilla and non-central tumors. Some studies did not find a relation between axillary status and APC involvement[6,40].

Some series evaluated prior radiotherapy and chemotherapy and did not consider these conditions as contraindications[41,42], even though other authors have observed a higher APC necrosis rate in previously irradiated patients.

A higher rate of APC tumoral involvement in patients with peritumoral lymphovascular invasion was found[43-48], reaching 35.6% in some studies.

When the histological type of tumor and its histological grade were evaluated, results of studies were conflicting, raising the need for more elaborated series for the conclusion of these subjects.

As for the overexpression of the Human Epidermal Growth Factor Receptor – type 2 (HER2), three studies showed APC involvement rate of around 19.7%, which was statistically significant[43,48,49].

The influence of estrogen and progesterone receptors was evaluated by a few studies. The largest of which was carried out by Weidong at al.[48], demonstrating greater rates of APC involvement in negative estrogen and progesterone receptor tumors.

A meta-analysis performed by Zhang et al.[50], evaluating 27 studies carried out between 1978 and 2014 with a total of 7,971 patients, showed that the most significant factors related to APC were: tumors >5 cm, positive axillary lymph nodes, tumor-APC distance <2.5 cm, stage III or IV, negative ER and PR, positive HER2 and carcinoma *in situ*.

Complications: despite having great advantages, NSM presents increased complications with operatory wound healing and necrosis[5,19,23,27,38,44]. The most frequent NSM complications are APC and cutaneous flaps necrosis. These complications have shown an important rate decrease due to the improvement of surgical techniques[12,14,18,19]. They currently have their incidence ranging from 0 to 19.5%[10]. Other complications found were hematoma and infection.

Reconstruction techniques: the main techniques for breast reconstruction in patients submitted to NSM are transitory or definitive implants and autologous flaps.

The criteria used to choose the type of reconstruction may be divided, in NSM cases, into: factors related to the tumor — location and proximity to the skin and the APC and the size of the tumor — and factors related to the patient — smoking, diabetes, body mass index (BMI), breast size, degree of ptosis, areola size and the patient's desire. Experience of the surgeon and the team should also be noted.

With the evolution of implants and expanders, the use of these materials in breast reconstruction is ever-widening. Endara et al.[30], in a recent review, observed from 6,615 NSM procedures, the occurrence of 2,373 (45.5%) reconstructions with expander followed by definitive implant, 2,126 (40.7%) reconstructions with definitive implant at once and 719 (13.8%) reconstructions with autologous flaps.

Another option is the use of expansive prostheses with the purpose of reconstructing at once, thus favoring postoperative adjustments in implant volume and contralateral symmetry[17,26].

The main autologous flaps used are: large dorsal flap, transverse rectus abdominis muscle flap (TRAM), free rectus abdominis

muscle flap and free gluteal muscle flap. Negative factors are: morbidity in the donation area, surgeries demanding greater expertise of the surgeon and the team, and longer length of surgery. Good tolerability to radiotherapy and a satisfactory long-term outcome — similar to those of non-operated breasts — are the main favorable points.

CONCLUSION

NSM has gained space as treatment of choice along with the highest number of breast cancer diagnoses in initial stages, with the objective of satisfactory aesthetic results. A current trend is seen in several institutions towards the acceptance of this technique when risk-reducing mastectomies are desirable and also when it is necessary to treat breast cancer. In order to achieve optimal results with this technique, a multidisciplinary action is required of the breast surgeon, the oncologist clinician and the radiotherapist. This technique presents excellent oncologic safety and low complication rates when careful selection of patients associated with the surgeon's expertise is ensured. However, larger series and longer-term follow-ups of patients submitted to NSM are still necessary.

REFERENCES

1. Toth BA, Lappert P. Modified skin incisions for mastectomy: the need for plastic surgical input in preoperative planning. Plast Reconstr Surg. 1991;87:1048-53.
2. Kroll SS, Ames F, Singletary SE, Schusterman MA. The oncologic risks of skin preservation at mastectomy when combined with immediate reconstruction of the breast. Surg Gynecol Obstet. 1991;172:17-20.
3. Singletary SE. Skin-sparing mastectomy with immediate breast reconstruction: the M. D. Anderson Cancer Center experience. Ann Surg Oncol. 1996;3:411-6.
4. Jabor MA, Shayani P, Collins DR, Karas T, Cohen BE. Nipple-areola reconstruction: satisfaction and clinical determinants. Plast Reconstr Surg. 2002;110:457-63;discussion 464-5.
5. Freeman BS. Subcutaneous mastectomy for benign breast lesions with immediate or delayed prosthetic replacement. Plast Reconstr Surg Transplant Bull. 1962;30:676-82.
6. Garcia-Etienne CA, Cody III HS, Disa JJ, Cordeiro P, Sacchini V. Nipple-sparing mastectomy: initial experience at the Memorial Sloan-Kettering Cancer Center and a comprehensive review of literature. Breast J. 2009;15:440-9. http://doi.org/10.1111/j.1524-4741.2009.00758.x
7. Boneti C, Yuen J, Santiago C, Diaz Z, Robertson Y, Korourian S, et al. Oncologic safety of nipple skin-sparing or total skin-sparing mastectomies with immediate reconstruction. J Am Coll Surg. 2011;212:686-93;discussion 693-95. http://doi.org/10.1016/j.jamcollsurg.2010.12.039
8. Caruso F, Ferrara M, Castiglione G, Trombetta G, De Meo L, Catanuto G, et al. Nipple sparing subcutaneous mas- tectomy: sixty-six months follow-up. Eur J Surg Oncol. 2006;32:937-40. https://doi.org/10.1016/j.ejso.2006.05.013
9. Chen CM, Disa JJ, Sacchini V, Pusic AL, Mehrara BJ, Garcia-Etienne CA, et al. Nipple-sparing mastectomy and immediate tissue expander/implant breast reconstruction. Plast Reconstr Surg. 2009;124:1772-80. https://doi.org/10.1097/PRS.0b013e3181bd05fd
10. De Alcantara Filho P, Capko D, Barry JM, Morrow M, Pusic A, Sacchini VS. Nipple-sparing mastectomy for breast cancer and risk-reducing surgery: the Memorial Sloan-Kettering Cancer Center experience. Ann Surg Oncol. 2011;18:3117-22. https://doi.org/10.1245/s10434-011-1974-y
11. Garcia-Etienne CA, Borgen PI. Update on the indications for nipple-sparing mastectomy. J Support Oncol. 2006;4:225-30.
12. Jensen JA, Orringer JS, Giuliano AE. Nipple-sparing mastectomy in 99 patients with a mean follow-up of 5 years. Ann Surg Oncol. 2011;18:1665-70. https://doi.org/10.1245/s10434-010-1475-4
13. Komorowski AL, Zanini V, Regolo L, Carolei A, Wysocki WM, Costa A. Necrotic complications after nipple- and areola-sparing mastectomy. World J Surg. 2006;30:1410-3. https://doi.org/10.1007/s00268-005-0650-4
14. Regolo L, Ballardini B, Gallarotti E, Scoccia E, Zanini V. Nipple sparing mastectomy: an innovative skin incision for an alternative approach. Breast. 2008;17:8-11. https://doi.org/10.1016/j.breast.2007.07.040
15. Sacchini V, Pinotti JA, Barros AC, Luini A, Pluchinotta A, Pinotti M, et al. Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? J Am Coll Surg. 2006;203:704-14. https://doi.org/10.1016/j.jamcollsurg.2006.07.015
16. Stolier AJ, Sullivan SK, Dellacroce FJ. Technical considerations in nipple-sparing mastectomy: 82 consecutive cases without necrosis. Ann Surg Oncol. 2008;15:1341-7. https://doi.org/10.1245/s10434-007-9753-5
17. Munhoz AM, Aldrighi C, Montag E, Arruda EG, Aldrighi JM, Filassi JR, et al. Periareolar skin-sparing mastectomy and latissimus dorsi ap with biodimensional expander implant reconstruction: surgical planning, outcome, and complications. Plast Reconstr Surg. 2007;119:1637-149;discussion 1650-2. https://doi.org/10.1097/01.prs.0000246406.68739.e4
18. Nava MB, Cortinovis U, Ottolenghi J, Riggio E, Pennati A, Catanuto G, et al. Skin-reducing mastectomy. Plast Reconstr Surg. 2006;118:603-10;discussion 611-3. https://doi.org/10.1097/01.prs.0000233024.08392.14
19. Tokin C, Weiss A, Wang-Rodriguez J, Blair SL. Oncologic safety of skin-sparing and nipple-sparing mastectomy: a discussion and review of the literature. Int J Surg Oncol. 2012;2012:921821. https://doi.org/10.1155/2012/921821

20. Cense HA, Rutgers EJ, Lopes Cardozo M, Van Lanschot JJ. Nipple-sparing mastectomy in breast cancer: A viable option? Eur J Surg Oncol. 2001;27:521-6. https://doi.org/10.1053/ejso.2001.1130

21. Mosahebi A, Ramakrishnan V, Gittos M, Collier J. Aesthetic outcome of different techniques of reconstruction following nipple-areola-preserving envelope mastectomy with immediate reconstruction. Plast Reconstr Surg. 2007;119:796-803. https://doi.org/10.1097/01.prs.0000251999.52374.09

22. Radovanovic Z, Radovanovic D, Golubovic A, Ivkovic-Kapicl T, Bokorov B, Mandic A. Early complications after nipple-sparing mastectomy and immediate breast reconstruction with silicone prosthesis: Results of 214 procedures. Scand J Surg. 2010;99:115-8. https://doi.org/10.1177/145749691009900302

23. Spear SL, Willey SC, Feldman ED, Cocilovo C, Sidawy M, Al-Attar A, et al. Nipple-sparing mastectomy for prophylactic and therapeutic indications. Plast Reconstr Surg. 2011;128:1005-14. https://doi.org/10.1097/PRS.0b013e31822b6456

24. Blechman KM, Karp NS, Levovitz C, Guth AA, Axelrod DM, Shapiro RL, et al. The lateral inframammary fold in- cision for nipple-sparing mastectomy: outcomes from over 50 immediate implant-based breast reconstructions. Breast J. 2013;19:31-40. https://doi.org/10.1111/tbj.12043

25. Crowe JP, Patrick RJ, Yetman RJ, Djohan R. Nipple-sparing mastectomy update: One hundred forty-nine procedures and clinical outcomes. Arch Surg. 2008;143:1106-10;discussion 1110. https://doi.org/10.1001/archsurg.143.11.1106

26. Munhoz AM, Aldrighi C, Montag E, Arruda E, Aldrighi JM, Filassi JR, et al. Optimizing the nipple-areola sparing mastectomy with double concentric periareolar incision and biodimensional expander-implant reconstruction: aesthetic and technical renements. Breast. 2009;18:356-67. https://doi.org/10.1016/j.breast.2009.09.008

27. Munhoz AM, Aldrighi CM, Montag E, Arruda EG, Aldrighi JM, Gemperli R, et al. Clinical outcomes following nipple-areola-sparing mastectomy with immediate implant-based breast reconstruction: a 12-year experience with an analysis of patient and breast-related factors for complications. Breast Cancer Res Treat. 2013;140:545-55. https://doi.org/10.1007/s10549-013-2634-7

28. Rivolin A, Kubatzki F, Marocco F, Martincich L, Renditore S, Maggiorotto F, et al. Nipple-areola complex sparing mastectomy with periareolar pexy for breast cancer patients with moderately ptotic breasts. J Plast Reconstr Aesthet Surg. 2012;65:296-303. https://doi.org/10.1016/j.bjps.2011.09.023

29. Salibian AH, Harness JK, Mowlds DS. Inframammary approach to nipple-areola-sparing mastectomy. Plast Reconstr Surg. 2013;132:700e-8e. https://doi.org/10.1097/PRS.0b013e3182a4d64f

30. Endara M, Chen D, Verma K, Nahabedian MY, Spear SL. Breast reconstruction following nipple-sparing mastectomy: a systematic review of the literature with pooled analysis. Plast Reconstr Surg. 2013;132:1043-54. https://doi.org/10.1097/PRS.0b013e3182a48b8a

31. Yang SJ, Eom JS, Lee TJ, Ahn SH, Son BH. Recipient vessel selection in immediate breast reconstruction with free abdominal tissue transfer after nipple-sparing mastectomy. Arch Plast Surg. 2012;39:216-21. https://dx.doi.org/10.5999%2Faps.2012.39.3.216

32. Chung AP, Sacchini V. Nipple-sparing mastectomy: where are we now? Surg Oncol. 2008;17:261-6. https://dx.doi.org/10.1016/j.suronc.2008.03.004

33. Sahin I, Isik S, Alhan D, Yıldız R, Aykan A, Ozturk E. One-staged silicone implant breast reconstruction following bi-lateral nipple-sparing prophylactic mastectomy in patients at high-risk for breast cancer. Aesthetic Plast Surg. 2013;37:303-11. https://dx.doi.org/10.1007/s00266-012-0044-6

34. Patani N, Mokbel K. Oncological and aesthetic considerations of skin-sparing mastectomy. Breast Cancer Res Treat. 2008;111:391-403. https://doi.org/10.1007/s10549-007-9801-7

35. Singletary SE, Robb GL. Oncologic safety of skin-sparing mastectomy. Ann Surg Oncol. 2003;10:95-7.

36. Andersen JA, Pallesen RM. Spread to the nipple and areola in carcinoma of the breast. Ann Surg. 1979;189:367-72.

37. Vyas JJ, Chinoy RF, Vaidyat JS. Prediction of nipple and areola involvement in breast cancer. Eur J Surg Oncol. 1998;24:15-6.

38. Simmons RM, Brennan M, Christos P, King V, Osborne M. Analysis of nipple/areolar involvement with mastectomy: Can the areola be preserved? Ann Surg Oncol. 2002;9:165-8.

39. Laronga C, Kemp B, Johnston D, Robb GL, Singletary SE. The incidence of occult nipple-areola complex involvement in breast cancer patients receiving a skin-sparing mastectomy. Ann Surg Oncol. 1999;6:609-13.

40. Petit JY, Veronesi U, Orecchia R, Rey P, Didier F, Giraldo A, et al. The nipple-sparing mastectomy: Early results of a feasibility study of a new application of perioperative radiotherapy (ELIOT) in the treatment of breast cancer when mastectomy is indicated. Tumori. 2003;89:288-91.

41. Blechman KM, Karp NS, Levovitz C, Guth AA, Axelrod DM, Shapiro RL, et al. The lateral inframammary fold incision for nipple-sparing mastectomy: Outcomes from over 50 immediate implant-based breast reconstructions. Breast J. 2013;19:31-40. https://doi.org/10.1111/tbj.12043

42. Wang J, Xiao X, Wang J, Iqbal N, Baxter L, Skinner KA, et al. Predictors of nipple-areolar complex involvement by breast carcinoma: Histopathologic analysis of 787 consecutive therapeutic mastectomy specimens. Ann Surg Oncol. 2012;19:1174-80. https://doi.org/10.1245/s10434-011-2107-3

43. Brachtel EF, Rusby JE, Michaelson JS, Chen LL, Muzikansky A, Smith BL, et al. Occult nipple involvement in breast cancer: Clinicopathologic findings in 316 consecutive mastectomy specimens. J Clin Oncol. 2009;27:4948-54. https://doi.org/10.1200/JCO.2008.20.8785

44. Gulben K, Yildirim E, Berberoglu U. Prediction of occult nipple-areola complex involvement in breast cancer patients. Neoplasma. 2009;56:72-5.

45. Vyas JJ, Chinoy RF, Vaidyat JS. Prediction of nipple and areola involvement in breast cancer. Eur J Surg Oncol. 1998;24:15-6.

46. Khan K, Chakraborti S, Mondal S. Morphological predictors of nipple areola involvement in malignant breast tumors. Indian J Pathol Microbiol. 2010;53:232-7. https://doi.org/10.4103/0377-4929.64329

47. Vlajcic Z, Zic R, Stanec S, Lambasa S, Petrovecki M, Stanec Z. Nipple-areola complex preservation: Predictive factors of neoplastic nipple-areola complex invasion. Ann Plast Surg. 2005;55:240-4.

48. Weidong L, Wang S, Guo X, Lang R, Fan Y, Gu F, et al. Nipple involvement in breast cancer: Retrospective analysis of 2323 consecutive mastectomy specimens. Int J Surg Pathol. 2011;19:328-34. https://doi.org/10.1177/1066896911399279

49. Pirozzi PR, Rossetti C, Carelli I, Ruiz CA, Pompei LM, Piato S. Clinical and morphological factors predictive of occult involvement of the nipple-areola complex in mastectomy specimens. Eur J Obstet Gynecol Reprod Biol. 2010;148:177-81. https://doi.org/10.1016/j.ejogrb.2009.10.021

50. Zhang H, Li Y, Moran MS, Haffty BG, Yang Q. Predictive factors of nipple involvement in breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2015;151:239-49. https://doi.org/10.1007/s10549-015-3385-4

REVIEW ARTICLE
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RELATIONSHIP BETWEEN OBESITY AND BREAST CANCER

Relação entre obesidade e câncer de mama

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ABSTRACT

Obesity is a growing clinical condition around the world, considered a risk factor for numerous diseases such as hypertension, myocardial infarction, diabetes, and cancer. Among the neoplasms related to overweight, breast cancer stands out. Therefore, the objective of this review is to elucidate the impact of obesity on the most prevalent cancer among women, either as a direct risk factor for its onset or as a determinant of survival.

KEYWORDS: obesity; cancer; breast cancer; risk factor.

RESUMO

A obesidade aponta como condição clínica em ascensão pelo mundo, considerada fator de risco para inúmeras doenças como hipertensão, infarto, diabetes e câncer. Dentre as neoplasias relacionadas com o excesso de peso, destaca-se o câncer de mama. O objetivo desta revisão é, portanto, elucidar o impacto que a obesidade causa no câncer mais prevalente entre as mulheres, seja como fator de risco direto para seu aparecimento, seja como determinante na sobrevida.

PALAVRAS-CHAVE: obesidade; câncer; câncer de mama; fator de risco.

Study conducted at Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo – Ribeirão Preto (SP), Brazil.
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INTRODUCTION

Obesity causes a chronic state of systemic inflammation, which in turn is one of the conditions for the development of several types of neoplasms, including breast cancer[1-3]. Data from the Brazilian Association for the Study of Obesity and Metabolic Syndrome (*Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica* - ABESO) in 2013 indicate that approximately 56% of Brazilians are overweight[4]. Around 20% of this group are obese, that is, their body mass index (BMI) is greater than or equal to 30 kg/m^2. This percentage is increasing around the world, which is alarming since overweight alone is responsible for many diseases, such as hypertension, diabetes, myocardial infarction, dyslipidemia, and cancer. In the United States of America (USA), this situation is even more critical, with approximately 40% of the population considered obese[5]. The risk of breast cancer for obese post-menopausal women has been well defined, as expounded below, but for pre-menopausal women, it is still being established, covering only some histological subtypes such as the triple-negative[6]. Risks of recurrence and death also increased in the subgroup of patients who already were obese at diagnosis, seeming more determinant for women with BMI above 35 kg/m^2[2,7].

DISCUSSION

Overweight and obesity have been associated with increased risk of hormone positive breast cancer (presence of progesterone and/or estrogen receptors) in post-menopause. On the other hand, the most consistent studies on pre-menopause show an inverse relationship between overweight, obesity, and the incidence of breast cancer in general[6,8], although the risk of the triple-negative histopathological subtype has been rising in this population. Such data have caused a strong impact on the Medical Society, which, in 2012, at the annual meeting between several North American medical entities, including the National Cancer Institute, concluded that obesity is responsible for a relative risk of 1.25 of developing breast cancer in post-menopause[9]. This same report established that physical activities and other weight loss efforts should be encouraged to avoid the growth of neoplasms in the USA.

A randomized clinical trial conducted by the North American group Women's Health Initiative (WHI), involving a 13-year follow-up of post-menopausal women, aged 50 to 79 years, showed a linear relationship between the risk of developing breast cancer and the various categories of body mass index ($p<0.001$)[6]. The group of women with BMI above 35 kg/m2 showed the strongest association. Their risk of developing invasive breast cancer was 58% higher compared to women with BMI lower than 25 kg/m^2. This same study analyzed a subgroup of women who developed breast tumors histologically positive for estrogen and progesterone receptors. The risk of developing this specific tumor was 56% higher among grade I obese women (BMI between 30 and 35 kg/m^2) and 86% among grade II obese women (BMI above 35 kg/m^2) when compared to women with normal BMI, according to the categorization of the study. The growth of estrogen receptor positive tumors is under the direct influence of estrogen levels, which are higher in overweight and obese post-menopausal women[10,11]. This scenario is the result of the facilitated aromatization of androstenedione and testosterone into estrogens in the adipose tissue[12,13].

Still on the WHI study[6], we highlight an important fact: women who started the follow-up with BMI below 25 kg/m^2 and had a weight gain of 5% above usual had a relative risk of 1.36 of developing invasive breast cancer when compared to women who maintained a stable weight. Besides the role of aromatization in carcinogenesis, the inflammatory behavior of adipocytes stands out. These two potential causes might explain the increased risk of breast cancer in the specific population who gained weight. The result suggests that preventing weight gain in healthy women can reduce their risk of developing breast cancer.

In contrast, the same study could not determine if there was an increase or decrease in the risk of breast cancer for subgroups of overweight and obese women who gained or lost weight during the follow-up. As this is not a specific study to analyze weight loss and its effects, we could not draw inferences about these results, not least because an unintended weight loss might have occurred. The conclusion from this research is that further well-designed studies aimed at this weight loss strategy are necessary.

Death specifically related to breast cancer in the group with BMI above 35 kg/m^2 was also twice as high than in the one with normal BMI. In addition, obesity has been associated with tumors having a larger diameter, presence of nodal disease, and distant metastases at diagnosis[6].

Recently, two large meta-analyses[14,15] skillfully described the negative influence of obesity on the survival of breast cancer patients, but with limitations, since the patient samples were heterogeneous, and the degree of obesity was not determined.

A recent observational study[16] that analyzed 18,967 women with a 10-year follow-up revealed a higher risk of distant metastasis at diagnosis when their BMI was greater than or equal to 30 kg/m^2. The risk of developing distant metastasis after 10 years of follow-up and dying of breast cancer after 30 years of being diagnosed was 46 and 38%, respectively, for women with BMI greater than or equal to 30 kg/m^2 when compared to those with BMI lower than 25 kg/m^2.

A retrospective analysis of a randomized phase III clinical trial called SUCCESS[17], involving more than 3,700 patients, verified the influence of obesity on people with high-risk breast cancer, with a follow-up of 65 months. The definition of high-risk adopted was: histologically positive axillary lymph node metastasis (pN1-N3) or node-negative breast cancer with tumor size greater than or equal to pT2, grade 3, negative hormone receptor status, or age

lower than 35 years. The mean patient age was 53 years, ranging from 21 to 86 years.

In this study, severely obese patients (BMI greater than or equal to 40 kg/m^2) had worse disease-free survival and overall survival rates, with a relative risk of 2.70 and 2.79, respectively, when compared to patients with normal weight. It is noteworthy that the study separated patients according to BMI in normal weight/underweight (BMI lower than 25 kg/m^2), overweight (between 25 and 29.9 kg/m^2), slightly obese (between 30 and 34.9 kg/m^2), moderately obese (between 35 and 39.9 kg/m^2), and severely obese (greater than 40 kg/m^2). Besides severely obese patients, no other subgroup was statistically significant in relation to worse progression-free survival and overall survival.

In general, epidemiological studies[18,19] show that obesity is a protective factor for breast cancer in pre-menopause. For young women, the ovary is the main source of circulating estrogens. As obesity would cause less frequent and irregular menstrual cycles, women would have less systemic exposure to estrogen, which would reduce their risk of developing hormone receptor positive tumors[20,21]. Corroborating this hypothesis, a recent study that retrospectively analyzed 2,659 women diagnosed with invasive breast cancer showed that this protection might occur in cases of luminal A tumors, that is, obese women would have a lower chance of developing tumors with this histological subtype[22]. However, a subgroup analysis of the same study showed a positive relationship between obesity and triple-negative breast cancer in pre-menopause. For each 5 kg/m^2 increase in BMI, the risk of developing a triple-negative tumor rose 16%. Regarding post-menopausal women, for each 5 kg/m^2 increase in BMI, there was a decrease of 9 and 16% in the risk of triple-negative and HER2 positive tumors, respectively, but a higher chance of developing a hormone receptor positive tumor.

Even though three other large studies[23-25] did not show a statistically significant relationship, their results tended to suggest an increased risk of triple-negative breast cancer for young obese women, in contrast to the findings of the study cited above.

Works such as these, which study histopathological subtypes in breast cancer and determine the various degrees of obesity, show us that overweight alone cannot be considered an isolated risk factor for breast cancer since the menopausal status and degree of obesity are crucial for conclusions about each specific case.

With the advances in breast cancer diagnosis and treatment, patient survival has increased, so researches are turning to lifestyle changes as a way to avoid its recurrence and improve overall survival. Based on this assumption, a recent systematic review[26] emphasized the importance of combining diet with physical activity for weight loss and gain in quality of life. Didactically, this review lists in a table the main dietary and physical activity recommendations for patients survivors of breast cancer.

The ENERGY[27] study is a multicenter intervention trial with 692 breast cancer survivors who had received treatment for their tumor at least two years previously, including patients on hormone therapy. Patients were separated into two groups. One adopted a more interventionist approach, with customized newsletters about how to lose weight and phone advice, while the other group had less intensive assistance. After 12 months, the intervention group presented a mean weight loss of 6%, while in the control group, the loss was 1.5% ($p<0.001$). Data on recurrence-free survival and overall survival are still not available for this work, but the authors suggest that weight loss causes lower circulating levels of estrogens and cytokines, markers involved in worse general prognosis for breast cancer patients.

A multicenter randomized clinical trial called DIANA[28], which is currently in progress, intends to answer more appropriately whether changes in the lifestyle of overweight or obese survivors of breast cancer can result in less recurrence and better overall survival. The intervention group will be supervised on weekly physical activities and dietary adjustments, such as reduced intake of saturated fat, animal protein (except fish), and high glycemic index foods, and increase in the consumption of fruits and vegetables, with a focus on weight loss.

Regarding drug intervention, some studies[29-31] used metformin in obese non-diabetic breast cancer patients, but these works have methodological and phase II flaws, not allowing the drawing of conclusions that could change the medical practice at the moment. Many of these studies showed that administration of metformin decreased levels of glycated hemoglobin and insulin, indirect markers of inflammatory response.

CONCLUSION

Obesity is increasing around the world, becoming the cause of numerous cardiovascular diseases, in addition to being responsible for several types of neoplasms, particularly breast cancer, the most prevalent among women. Until a short time ago, obesity was considered a risk factor for breast cancer in post-menopausal women and worked as a protective factor for those in pre-menopause. However, recent studies have provided more detailed data, as demonstrated in this review. We underline the fact that severe obesity (BMI above 35 kg/m^2) leads to an increased risk of breast cancer for post-menopausal women when compared to grade I obesity (BMI between 30 and 34.9 kg/m^2), overweight (BMI between 25 and 29 kg/m^2) and normal weight/underweight (BMI below 25 kg/m^2).

Similarly, severely obese women receive more diagnosis of tumors with a larger diameter, nodal disease, and distant metastasis. With respect to pre-menopause, obesity has been increasingly associated with histologically triple-negative tumors, of worse prognosis. Considering these data, interventional studies have been developed to assist breast cancer survivors in losing weight and improving their life quality. Even though they present favorable data concerning weight loss, we need further

studies with wider sampling and long follow-up to draw definitive conclusions about gain in disease-free survival and overall survival. At any rate, all health professionals who follow breast cancer patients must recommend adjustments to their diet with reduced intake of saturated fat, animal protein (except fish), and high glycemic index foods, and higher consumption of fruits and vegetables, as well as physical activity monitored by a qualified physical educator.

REFERENCES

1. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454:436-44. https://doi.org/10.1038/nature07205
2. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. Nat Rev Cancer. 2015;15:484-98. https://doi.org/10.1038/nrc3967
3. Park J, Morley TS, Kim M, Clegg DJ, Scherer PE. Obesity and cancer-mechanisms underlying tumour progression and recurrence. Nat Rev Endocrinol. 2014;10:455-65. https://doi.org/10.1038/nrendo.2014.94
4. Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. Quase 60% dos brasileiros estão acima do peso [Internet]. 2015 [acesso em 21 ago. 2015]. Disponível em: http://www.abeso.org.br/noticia/quase-60-dos-brasileiros-estao-acima-do-peso-revela-pesquisa-do-ibge
5. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. J Am Med Assoc. 2012;307:491-7. https://doi.org/10.1001/jama.2012.39
6. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, et al. Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the Women's Health Initiative randomized clinical trials. JAMA Oncol. 2015;1:611-21. https://doi.org/10.1001/jamaoncol.2015.1546
7. Pajares B, Pollán M, Martín 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. Breast Cancer Res. 2013;15:R105. https://doi.org/10.1186/bcr3572
8. Moley KH, Colditz GA. Effects of obesity on hormonally driven cancer in women. Sci Transl Med. 2016;8:323ps3. https://doi.org/10.1126/scitranslmed.aad8842
9. Eheman C, Henley SJ, Ballard-Barbash R, Jacobs EJ, Schymura MJ, Noone AM, et al. Annual Report to the Nation on the status of cancer, 1975–2008, featuring cancers associated with excess weight and lack of sufficient physical activity. Cancer. 2012;118(9):2338-66. https://doi.org/10.1002/cncr.27514
10. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nature Reviews. Cancer. 2011;11(12):886-95. https://doi.org/10.1038/nrc3174
11. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev. 2004;13(10):1558-68.
12. Goodwin PJ. Obesity and endocrine therapy: host factors and breast cancer outcome. Breast. 2013;22(Supl. 2):S44-7. https://doi.org/10.1016/j.breast.2013.07.008
13. Morris PG, Hudis CA, Giri D, Morrow M, Falcone DJ, Zhou XK, et al. Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. Cancer Prev Res. 2011;4(7):1021-9. https://doi.org/10.1158/1940-6207.CAPR-11-0110
14. Chan DSM, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan 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. https://doi.org/10.1093/annonc/mdu042
15. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat. 2010;123:627-35. https://doi.org/10.1007/s10549-010-0990-0
16. Ewertz M, Jensen MB, Gunnarsdóttir KÁ, Højris I, Jakobsen EH, Nielsen D, et al. Effect of obesity on prognosis after early-stage breast cancer. J Clin Oncol. 2011;29:25-3. https://doi.org/10.1200/JCO.2010.29.7614
17. Widschwendter P, Friedl TW, Schwentner L, DeGregorio N, Jaeger B, Schramm A, Bekes I, Deniz M, Lato K, Weissenbacher T, et al. The influence of obesity on survival in early, high-risk breast cancer: results from the randomized SUCCESS A trial. Breast Cancer Res 2015; 17:1-11. https://doi.org/ 10.1186/s13058-015-0639-3
18. Van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol. 2000;152:514-27.
19. Ursin G, Longnecker MP, Haile RW, Greenland S. A meta-analysis of body mass index and risk of premenopausal breast cancer on JSTOR. Epidemiology. 1995;6:137-41.
20. Kato I, Toniolo P, Koenig KL, Shore RE, Zeleniuch-Jacquotte A, Akhmedkhanov A, et al. Epidemiologic correlates with menstrual cycle length in middle aged women. Eur J Epidemiol. 1999;15:809-14.
21. Gerber M. Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. J Natl Cancer Inst. 1997;89:661-2. https://doi.org/10.1093/jnci/89.9.661
22. Chen L, Cook LS, Tang MT, Porter PL, Hill DA, Wiggins CL, Li CI. Body mass index and risk of luminal, HER2-overexpressing, and triple negative breast cancer. Breast Cancer Res Treat. 2016; 157:545-54. https://doi.org/10.1007/s10549-016-3825-9
23. Yang XR, Sherman ME, Rimm DL, Lissowska J, Brinton LA, Peplonska B, et al. Differences in risk factors for breast cancer molecular subtypes in a population based study. Cancer Epidemiol Biomark Prev. 2007;16:439-43. https://doi.org/10.1158/1055-9965.EPI-06-0806

24. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, Dressler LG, et al. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat. 2008;109:123-39. https://doi.org/10.1007/s10549-007-9632-6

25. Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, et al. Risk factors for triple negative breast cancer in women under the age of 45 years. Cancer Epidemiol Biomark Prev. 2009;18:1157-66. https://doi.org/10.1158/1055-9965.EPI-08-1005

26. Conwright CMD, Lee K, Kiwata JL. Reducing the Risk of Breast Cancer Recurrence: an Evaluation of the Effects and Mechanisms of Diet and Exercise. Curr Breast Cancer Rep. 2016;8:139-50. https://dx.doi.org/10.1007%2Fs12609-016-0218-3

27. Rock CL, Flatt SW, Byers TE, Colditz GA, Demark-Wahnefried W, Ganz PA, et al. Results of the exercise and nutrition to enhance recovery and good health for you (ENERGY) trial: a behavioral weight loss intervention in overweight or obese breast cancer survivors. J Clin Oncol Off J Am Soc Clin Oncol. 2015;33(28):3169-76. https://doi.org/10.1200/JCO.2015.61.1095

28. Villarini A, Pasanisi P, Traina A, Mano MP, Bonanni B, Panico S, et al. Lifestyle and breast cancer recurrences: the DIANA-5 trial. Tumori. 2012;98(1):1-18. https://doi.org/10.1700/1053.11494

29. Campagnoli C, Pasanisi P, Abbà C, Ambroggio S, Biglia N, Brucato T, et al. Effect of different doses of metformin on serum testosterone and insulin in non-diabetic women with breast cancer: a randomized study. Clin Breast Cancer. 2012;12(3):175-82. https://doi.org/10.1016/j.clbc.2012.03.004

30. Hadad S, Iwamoto T, Jordan L, Purdie C, Bray S, Baker L, et al. Evidence for biological effects of metformin in operable breast cancer: a pre-operative, window-of-opportunity, randomized trial. Breast Cancer Res Treat. 2011;128(3):783-94. https://doi.org/10.1007/s10549-011-1612-1

31. Ko KP, Ma SH, Yang JJ, Hwang Y, Ahn C, Cho YM, et al. Metformin intervention in obese non-diabetic patients with breast cancer: phase II randomized, double-blind, placebo controlled trial. Breast Cancer Res Treat. 2015;153(2):361-70. https://doi.org/10.1007/s10549-015-3519-8

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BREAST TOMOSYNTHESIS: A BETTER MAMMOGRAPHY

Tomossíntese mamária: uma mamografia melhor

Vera Lucia Nunes Aguillar[1]*, Selma di Pace Bauab[2], Aron Belfer[3]

ABSTRACT

Digital mammography is an excellent method for detecting breast cancer at an early stage, but overlap of breast structures may lead to both false-positive and false-negative results. The digital breast tomosynthesis (DBT) is addressed to overcome this limitation of conventional 2D mammography. The purpose of this study was to discuss the multiple aspects related to this new tool, including its role in breast cancer screening, through a literature review. DBT, or 3D mammography, provides a three-dimensional representation of the breast, with the ability to scroll through breast tissue in the reconstructed images, thereby reducing the effect of tissue superimposition. This leads to improved sensitivity and specificity in breast cancer screening. In diagnostic cases, tomosynthesis increases the accuracy with better characterization and localization of the lesions. Prospective and retrospective studies confirm that DBT is superior to digital mammography in breast cancer screening, with 27 to 53% increase in cancer detection and 17 to 37% reduction in false-positive recalls. A total of 40 to 49% of the cancers detected by DBT were invasive: 40 to 48% of histological grade 2 or 3 and more than 75% were node negative. DBT is the most promising new modality for breast cancer screening. Further studies are needed to evaluate the reduction of interval cancers with this modality.

KEYWORDS: mammography; mass screening; breast neoplasms.

RESUMO

Mamografia digital é um método excelente para detecção precoce do câncer de mama. Porém, a sobreposição das estruturas mamárias pode levar a resultados falso-positivos e falso-negativos. A tomossíntese mamária é dirigida para superar essa limitação da mamografia 2D convencional. O objetivo deste estudo é discutir os múltiplos aspectos relacionados a essa nova ferramenta, incluindo, através de uma revisão da literatura, seu papel no rastreamento do câncer de mama. A tomossíntese mamária, ou mamografia 3D, proporciona uma representação tridimensional da mama, com a habilidade de podermos visualizar as imagens reconstruídas em diversos planos, reduzindo o efeito da sobreposição. Isso conduz a uma melhora da sensibilidade e da especificidade no rastreamento mamográfico. Nos casos diagnósticos, aumenta a acurácia com melhor caracterização e localização das lesões. Estudos prospectivos e retrospectivos confirmam que, no rastreamento do câncer de mama, a tomossíntese mamária é superior à mamografia digital, com aumento da detecção de 27 a 53%, e na redução das reconvocações falso-positivas entre 17 e 30%. De 40 a 49% dos cânceres detectados pela tomossíntese foram invasivos: de 40 a 48% de grau histológico 2 ou 3 e mais de 75% foram linfonodo negativos. Tomossíntese mamária é a nova modalidade mais promissora para o rastreamento do câncer de mama. São necessários estudos adicionais com essa nova modalidade para a avaliação da redução dos cânceres de intervalo.

PALAVRAS-CHAVE: mamografia; programas de rastreamento; neoplasias da mama.

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INTRODUCTION

Breast tomosynthesis or 3D mammography is a technological advancement in digital mammography, which allows three-dimensional representation of breast tissue from two-dimentional projections. It was developed to overcome an important limitation of conventional digital mammography (2D), which is normal overlapping tissue during the acquisition of the radiographic image. This limitation of 2D mammography may lead to low sensitivity in detecting some cancers and high false-positive recall rates (due to summation images). Tomosynthesis reduces the impact of overlapping breast tissue by depicting tissue on a dynamic sequence of thin cross-sectional images which results in a considerable increase in diagnostic accuracy (Figure 1A)[1-4].

HOW IS TOMOSYNTHESIS OBTAINED?

Tomosynthesis uses a digital mammograph, in which the X-ray source moves in an arc above the compressed breast and a series of low-dose x-ray projections are acquired at different angles (Figure 1B). From these two-dimensional projections, 3D images (tomosynthesis slices) are reconstructed, with 1 mm thickness, parallel to the detector. The number of slices depends on breast thickness : thus, in a 5-cm breast, 50 slices per mammographic incidence are obtained. All images are analyzed in high resolution monitors, either individually or in cine mode (Figure 2)[4-6].

The are different commercially systems available with variations in scan angle, number of projections and scan time.

Exam technique

Patient positioning and breast compression at tomosynthesis are similar to that at DM, typically using standard craniocaudal and mediolateral oblique projections. The approval of tomosynthesis by the Food and Drug Administration (FDA), in the United States, in 2011, was based on the "combo mode": 3D images are obtained along with 2D DM images during the same compression. Although tomosynthesis is superior to detect non-calcified lesions (nodules and architectural distortions), the 2D images gives us a panoramic view of the breasts, which allows better analysis of asymmetries and comparison with previous examinations[3,4].

Similar to conventional mammography, two views of each breast are recommended with tomosynthesis, since some lesions may be seen only in one projection. Clinical studies have shown that about 9% of the tumors may be missed if only one incidence of tomosynthesis is used.

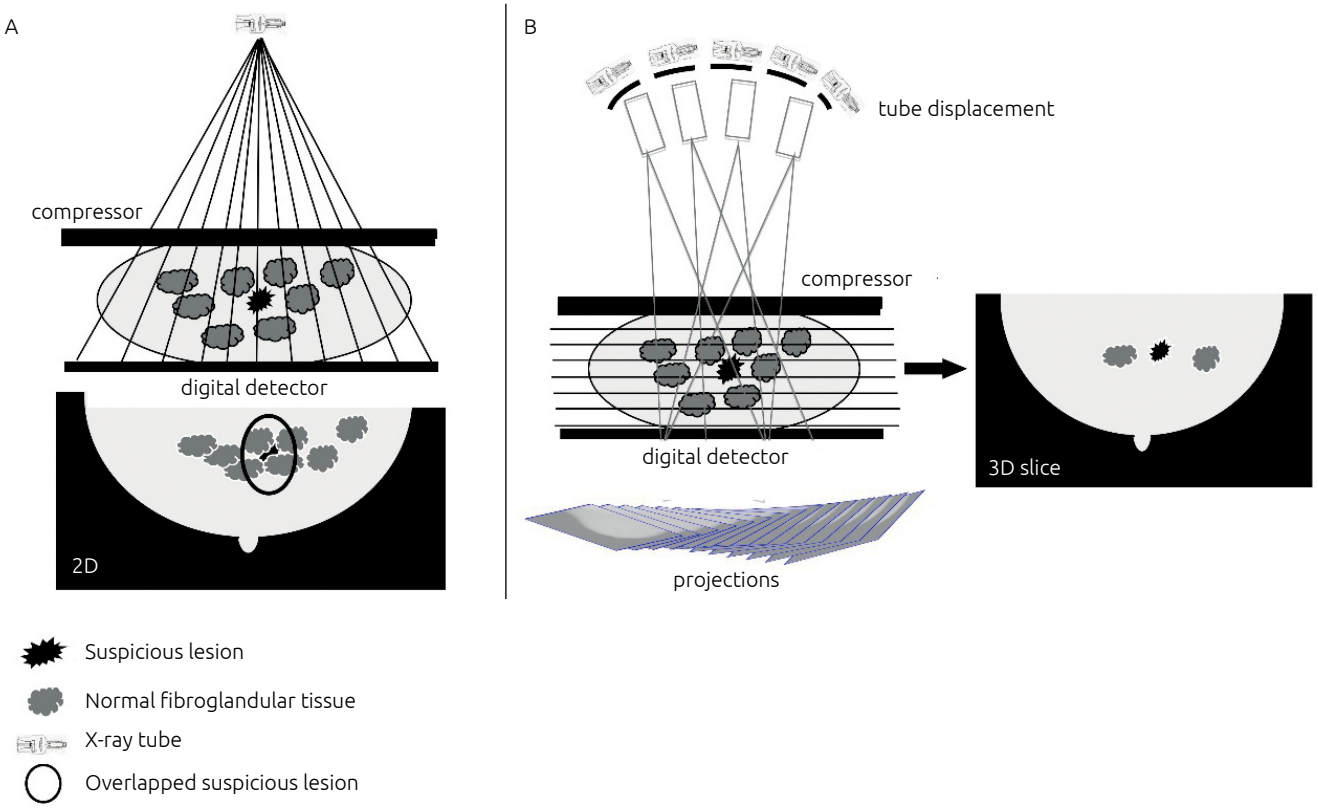


Figure 1. Schematic acquisition of mammographic images during breast compression: (A) conventional digital mammography (2D) shows overlap of normal structures and suspicious lesion; (B) tomosynthesis (3D) reduces tissue overlap by detecting the suspicious lesion in one of the slices.

Radiation dose

The disadvantage of combination of DM and tomosynthesis is an approximate twofold increase in radiation dose, although the total dose still falls within the safety limits determined by American and European regulatory agencies[7]. Concerns regarding increased radiation dose has led to other alternatives, such as:

1. Replace 2D mammography by SM (synthesized mammography), in combination with tomosynthesis. In this case, the performance of the combined test is similar, without increasing the total radiation dose[8-10];
2. Tomosynthesis with only one view, combined to 2D mammography [4,11]. However, this option can reduce sensitivity and especificity of the exam, when compared to tomosynthesis performed in two projections[11-13].

2D SYNTHESIZED MAMMOGRAPHY

Synthesized mammography (SM) is a technique that generates two-dimensional images from the DBT dataset, eliminating the need for a separately acquired FFDM examination and thereby decreasing the radiation dose to the patient. [8,10]. Although SM's initial version was not well accepted due to its limited technical quality, recent studies found that its updated version presented the same performance of the conventional 2D image. Although the mathematical algorithms to obtain synthesized images are different among the manufacturers, the objective is similar and consists in obtaining the information provided by 2D images – panoramic view of the breasts, comparison with previous mammograms and evaluation of microcalcifications - without extra dose of radiation. It is important to emphasize that the SM must be analyzed along with the tomosynthesis slices, never as an isolated study[10].

Breast anatomy in tomosynthesis

Although normal anatomy is similar in 2 D and 3Ds images, the reduction of overlapping tissue in the tomosynthesis slices allows better individualization of breast structures. In slices closest to the detector and the compressor, the dermis and cutaneous pores (round radiolucent images) and eventual cutaneous lesions, such as *nevi*, or calcifications are better seen. Cooper ligaments and linear structures in pre-parenchymal fat are seen brighter in tomosynthesis slices than in conventional mammography. The fibroglandular tissue is gray, with a lower density in relation to the 2D image, due to the smaller amount of breast tissue evidenced in each slice. High density objects, such as markers and metal clips and larger calcifications, may produce artifacts that, however, do not interfere with image interpretation. Tomosynthesis increase lesion conspicuity with better definition of margins and spicules, due to reduction in tissue overlapping.[3,4].

The characteristics of the parenchyma texture in the tomosynthesis correlate better with breast density than digital mammography, and may become a method of measuring breast density, resulting in a quantitative biomarker to estimate the risk of cancer.

SM presents its own characteristics, different from the conventional image: brighter mammary parenchyma, blurring of skin and subcutaneous tissue, loss of resolution of axillary area, pseudocalcifications and artifacts generated by clips or other high-density images. SM enhances linear structures - such as Cooper's ligaments or spicules associated with masses or architectural distortions - and increases brightness and contrast of calcifications. The extreme dense breasts (ACR D) appear brighter in the SM due to the summation of the tomosynthesis slices (Figure 3).

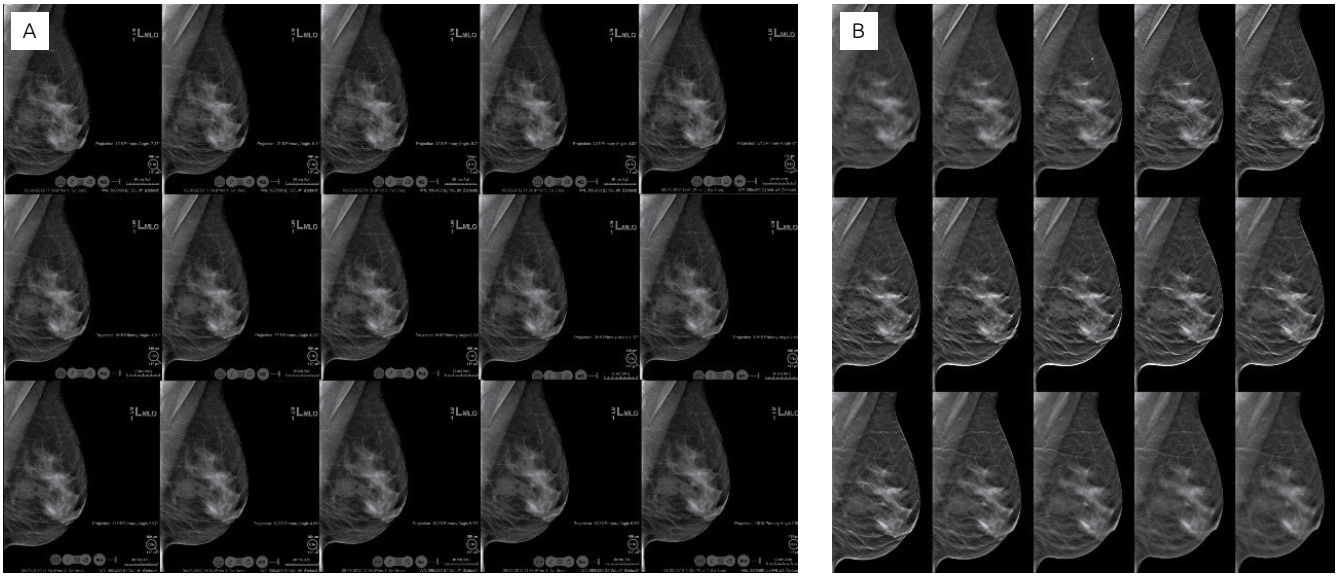


Figure 2. (A) Low-dose radiation projections; (B) from which 1 mm thick tomosynthesis slices are reconstructed.

Exam interpretation

Due to the large number of images obtained with tomosynthesis, the analysis of the exam must be performed in a systematic way, with implementation of a hanging protocol in the high-resolution monitor, to optimize reading time. Interpretation of the exam starts with the analysis of the 2D images (conventional or synthesized) for detection of calcifications, asymmetries, masses or architectural distortions. Next, a comparative analysis is performed with previous mammograms to characterize developing asymmetries or other new lesions. Tomosynthesis images are interpreted with two-dimensional mammography, using the latter as a "road map" for each mammographic incidence[1,4,14].

It is necessary to obtain conventional (2D) digital mammography along with tomosynthesis, since each method provides different types of information in the analysis of mammographic findings (Chart 1).

Tomosynthesis slices must be seen sequentially (cine mode), breast by breast and incidence by incidence. It is important to mentally divide the breast into 2 or 3 segments and look at each of them separately, during at least one cine mode cycle, to increase detection of small lesions[1,14].

Exam interpretation time

Tomosynthesis is an easy-to-implement technology because the examination is performed in the same way as conventional or digital mammography. However, interpretation time is longer due to a large number of images to be analyzed, which requires more concentration and focus from the radiologist, resulting in greater mental and visual fatigue[15,16]. One of the alternatives proposed to reduce interpretation time is to abolish the double reading of tomosynthesis examination, which, according to Houssami et al.[17], does not change the benefits of tomosynthesis (increase in detection of invasive cancer and reduction of false-positive recalls), compared to DM alone.

The learning curve and the optimization of reading time with the implementation of a flowchart in the monitor (report flow) are fundamental to reduce the time of interpretation in tracing[14]. The availability of computer-aided detection (CAD) systems for synthesized image and tomosynthesis slices and the use of thicker tomosynthesis images (slabs), instead of 1 mm slices, are alternatives for the reduction of interpretation time.

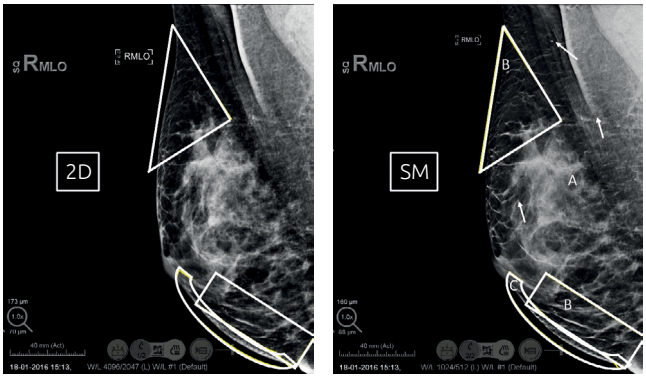


Figure 3. Comparison of 2D with synthesized mammography: in synthesized mammography (SM), there was an increase of the contrast with the parenchyma (A) with greater intensity (whiter), greater enhancement of the ligaments (B) and of the linear structures in pre-parenchymatous fat, greater prominence of calcifications (arrows). The increased intensity in the peripheral area of the image (C) dos not represent greater skin thickness and is associated to the reconstruction program, noticing lesser prominence in more recent versions.

IMPACT OF TOMOSYNTHESIS IN COMPUTER DEPARTMENTS

In tomosynthesis examination, the images of each slice generate the same volume of data as a 2D. The number of slices is proportional to breast thickness and usually 30 to 70 slices are obtained, with the total volume of data generated by the tomosynthesis, by incidence, significantly higher than in 2D. This fact has several implications for the storage of images.

The size of the tomosynthesis file also implies the time and speed of transmission and retrieval of the examination. Compaction softwares are used for better storage and transmission performance of tomosynthesis.

Chart 1. Degree of information provided by tomosynthesis and conventional digital mammography on different aspects in the analysis of the images.

	2D	Tomosynthesis
Visibility of lesions	++	+++
Margin analysis	+	+++
Location of the lesions		+++
Extent of the lesions		+++
Multifocality	+	+++
Density associated with calcifications		+++
Reduction of summation	+	+++
Recall reduction	+	+++
Asymmetries	+++	+
Interval changes	+++	+
Comparison with previous ones	+++	+
Calcifications (detection)	+++	++
Calcifications (distribution)	+++	+

+: low grade; ++: medium grade; +++: high grade.
Source: Rafferty and Belfer[15].

INDICATIONS OF TOMOSYNTHESIS

The indications for tomosynthesis are the same as for conventional digital mammography: it can be used as a diagnostic or screening test for early cancer detection. Due to the reduction of tissue overlap, tomosynthesis presents several advantages over the 2D, such as:

1. Increase in cancer detection rate (Figures 4, 5 and 6);
2. Reduction of false-positive recalls and additional mammographic projections, especially spot compression, which means reduction of the total dose of radiation (Figure 7);
3. Increase in the conspicuity of noncalcified lesions (masses, asymmetries and architectural distortions) (Figures 8, 9 and 10);
4. Reduction in the percentage of category 3 lesions (ACR BI-RADS), especially asymmetries;
5. Detection and location of lesions seen in only one incidence (Figures 11 and 12);
6. Confirm cutaneous lesions (Figure 13);

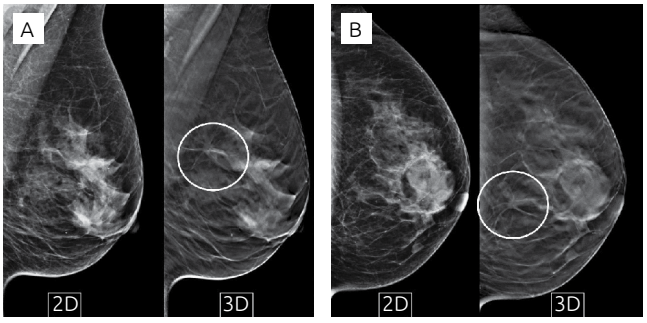


Figure 4. Conventional digital mammography (2D) and tomosynthesis representative slice (3D), 1 mm thick, evidenced spiculated nodule (circle): (A) mediolateral incidence; (B) craniocaudal incidence. Histology: invasive carcinoma.

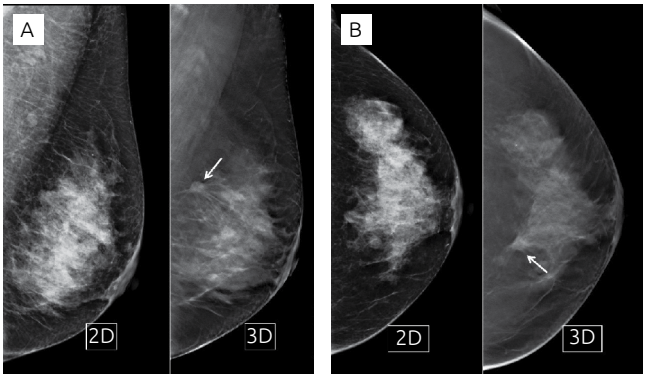


Figure 5. Conventional digital mammography (2D) and representative tomosynthesis slice (3D), 1 mm thick, evidenced spiculated nodule (arrows) identified only in tomosynthesis: (A) mediolateral incidence; (B) craniocaudal incidence. Histology: invasive carcinoma.

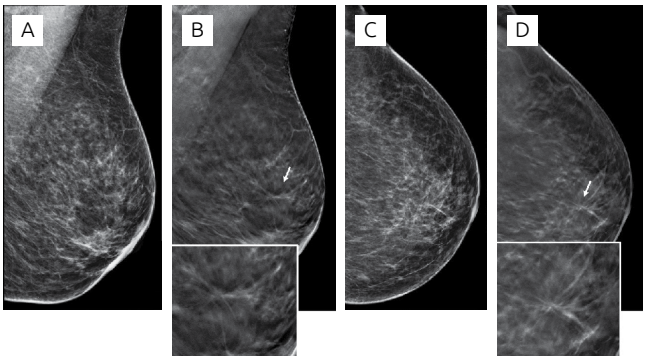


Figure 6. Architectural distortion (arrows and details) evidenced in tomosynthesis slices (B and D) and not expressed in 2D (A and C). Histology: invasive lobular carcinoma.

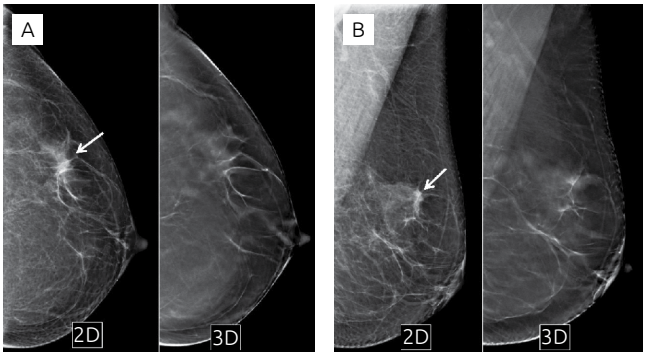


Figure 7. The density (arrows) observed in conventional digital mammography (2D) does not correspond to tomosynthesis slices (3D), representing overlap of normal tissues (pseudolesion): (A) craniocaudal incidence; (B) mediolateral incidence.

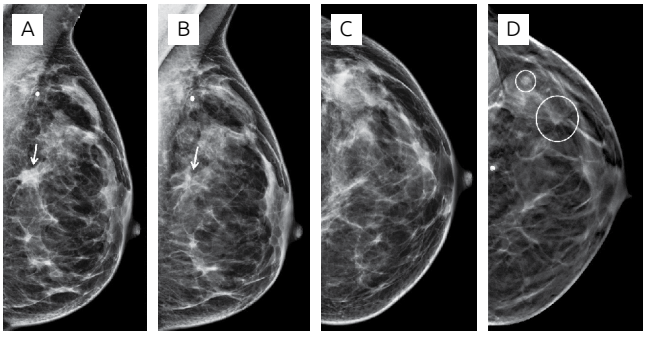


Figure 8. Patient was recalled for evaluation of irregular asymmetry in the upper/posterior third of her left breast (arrow), in the oblique mediolateral incidence in 2D (A). Tomosynthesis slice (B) was shown to be tissue overlap. In tomosynthesis slice, in craniocaudal incidence (D), an architectural distortion area (larger circle) was observed, not evidenced in 2D in craniocaudal incidence (C) and an irregular nodule (smaller circle) was better characterized in the same slice (D).

TOMOSYNTHESIS IN SCREENING

Performance of tomosynthesis in screening was investigated in a series of prospective, retrospective, single-institution or multi-center studies, all using 2D mammography along with tomosynthesis *versus* the 2D one alone. The first publications on tomosynthesis emphasized the reduction of the recall rate (15 to 37%) as its primary advantage[18,19]. The multicenter study, published by Rafferty et al. in 2013, was crucial in demonstrating that tomosynthesis, in addition to reducing the number of recalls, significantly increased the diagnostic accuracy in relation to 2D mammography[20].

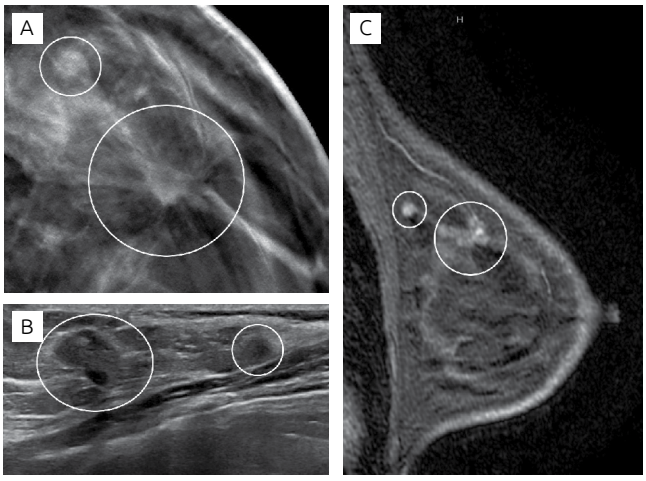


Figure 9. Correlation between tomosynthesis (A), ultrasonography (B) and magnetic resonance imaging (B) showing the nodule (smaller circle) and area of architectural distortion (larger circle).

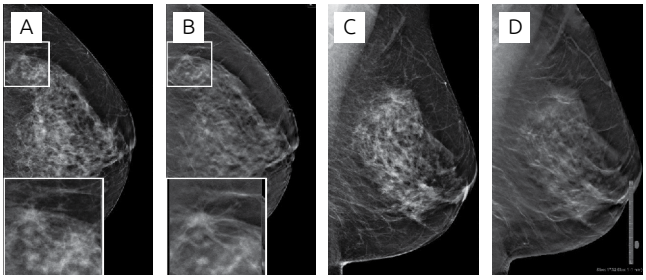


Figure 10. Nodule evidenced in craniocaudal incidence, in 2D (A) shows radiolucent center in tomosynthesis slice (B) and represents intramammary lymph node.

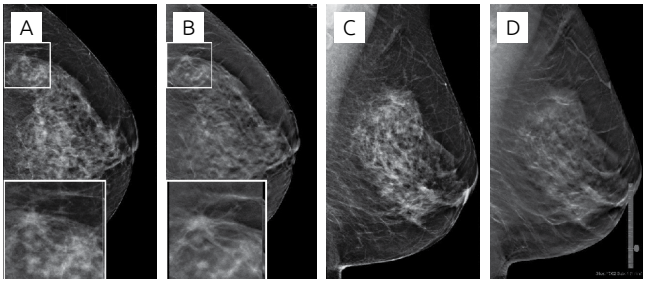


Figure 11. Finding observed only in craniocaudal incidence in 2D (A). Lesion's infiltrative margins are characterized in tomosynthesis slices in craniocaudal incidence (B). The lesion is not observed in 2D nor in tomosynthesis in mediolateral incidence (C and D). Histology: Invasive Lobular carcinoma grade I.

Prospective studies

Prospective clinical studies are all European, although they have different study designs. The largest one, carried out in Oslo (Oslo Tomosynthesis Screening Trial – OTST), used independent double reading and analyzed the first results in 12,631 women in the screening program at the University of Oslo, aged between 50 and 69, who performed 2D together with tomosynthesis, two views per breast and per modality. The combination of tomosynthesis and 2D increased the cancer detection rate by 27% compared

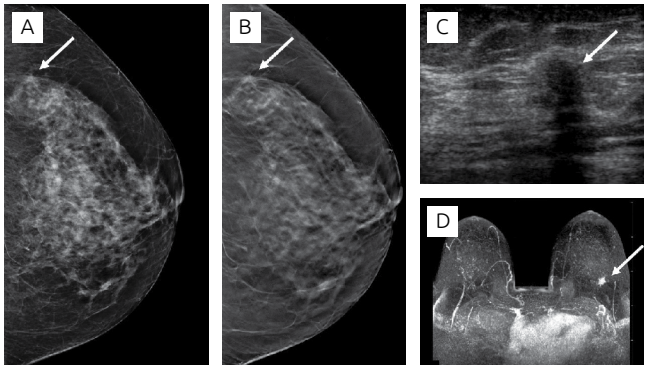
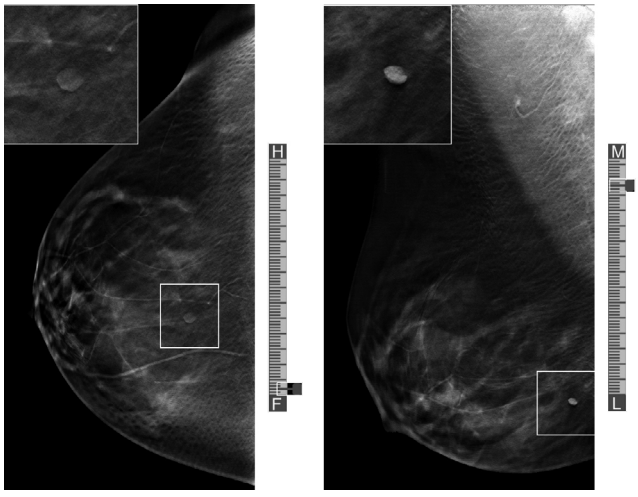


Figure 12. Correlation of the finding observed only in craniocaudal incidence in (A) and in tomosynthesis (B) with ultrasound (C) and with magnetic resonance imaging (D). Histology: Invasive Lobular carcinoma grade I.



H: head; F: feet; M: medial; L: lateral.

Figure 13. Location of the lesion in tomosynthesis. The lateral bar demonstrates the lesions are in the lower (F) and medial (M) quadrant, at the extremity of the bar, demonstrating the quadrant and its cutaneous location.

to 2D alone (absolute increase of 1.9 cancers/thousand women screened by tomosynthesis) and, at the same time, reduced the recall rate[17].

The Italian study (Screening with Tomosynthesis OR standard Mammography – STORM1), carried out in two cities Trento and Verona, included 7,292 women who did both - 2D and tomosynthesis – in two views per breast per modality, with double sequential reading. Their final results were promising: a relative increase of 53% in cancer detection with tomosynthesis (an increase of 2.8 cancers/thousand) and 17% fewer recalls[21].

STORM 2 is another population-based prospective study, based on STORM 1, which included 9,672 women. In this study, all patients were screened with 2D and tomosynthesis, and SM was also used: the combined examination, either with a 2D (COMBO mode) or with SM (TOMOHD mode), detected more cancers than the digital mammography alone. There was an increase of 35 and 40% (COMBO and TOMOHD, respectively) in cancer detection rate, with an increase of 2.2 and 2.5 cancers/thousand). However, there was a slight increase in false-positive recall with the combined examination, compared to 2D alone, especially with the use of SM[22].

The study performed in Malmö, Sweden (Malmö Breast Tomosynthesis Screening Trial – MBTST), differs from the previous ones because it was designed to evaluate the efficacy of only one view of tomosynthesis (mediolateral oblique) *versus* two views of 2D mammography (craniocaudal and MLO). The first results included 7,500 women, aged 40 to 74 years old, invited to perform both modalities. Tomosynthesis (in just one view-MLO) increased cancer detection rate by 43% (2.6 more cancers/1000 women). Although radiation dose was lower, there was an increase in the recall rate, probably due to the use of only one view of tomosynthesis[23].

In summary, prospective studies showed a 26 to 43% increase in cancer detection rate with the addition of tomosynthesis to 2D mammography, basically at the expense of invasive carcinomas. It is important to remember that these results reflect prevalent exams, that is, the first tomosynthesis examinations in these populations (Table 1)[24].

Retrospective studies

American studies on tomosynthesis are retrospective, comparing isolated 2D *versus* digital mammography associated with tomosynthesis. Some of them should be highlighted as pioneers: Rose et al.[19], with a 25% increase in cancer detection, in a private clinic; Haas et al.[18], with an increase of 10% in an academic center and reduction of recall rate from 37 to 30%. The work of McCarthy et al.[25] has, in fact, demonstrated the impact of tomosynthesis on screening after its implementation in a population in a single academic center in the United States. The screening was performed in all women, from October 2011 to February 2013 (n = 15,571 women) with a significant reduction in the number of recalls in the group with tomosynthesis. Overall, the increase in cancer detection was small (0.9 additional cancers/thousand women), but analysis of subgroup showed a significant increase in cancer detection among women younger than 50 years[25]. In 2014 , a large US retrospective multicenter study was published (13 academic or private institutions), including 281.187 women undergoing FFDM only and 173.663 women having 2D+ 3D . The results showed a 29% increase in cancer detection rate and 15% decrease of recalls, after implementation of tomosnthesis,.

In 2015, data from the TOMMY TRIAL (Comparison of TOMosynthesis with digital Mammography in the UK NHS Breast Screening Programme), a retrospective, multicenter study with the participation of several radiologists was published, comparing the performance of tomosynthesis and 2D *versus* isolated 2D in the mammography screening program of the United Kingdom. Women aged between 29 and 85 years (mean 56 years) were recruited from July 2011 to February 2013 and the final analysis consisted of 7,060 cases. All participants performed 2D (on two incidences) and tomosynthesis (on two

Table 1. Resultas obtained with prospective and retrospective studies in the screening of breast cancer.

Design of the study	Type of Reading	Population (n)	Age range (years)	Recall rate	Detection rate /1000 (2D)	Detection rate/1000 (tomosynthesis)	Relative carcinoma increase
Prospective paired	Sequential pair	7,292	48 to 71	-17%	5.3	8.1	53%
Prospective paired	Independent pair	12,631	50 to 69	-13%	6.1	8.0	27%
Prospective paired	Sequential pair	7,500	40 to 74	43%	6.3	8.9	43%
Prospective	Sequential pair	9,672	53 to 63	16%	6.3	8.8	35%
4 arms				30%	6.3	8.8	40%
Retrospective unpaired	Single reading	2D: 281,187 3D: 173,663		-16%	4.2	5.4	29%

incidences), with SM replacing 2D, as of 2011. The results showed increased specificity with tomosynthesis in all subgroups: age range, breast density and mammographic findings. Regarding sensitivity, tomosynthesis, compared with isolated 2D, was superior in dense breasts, invasive carcinomas of 11 to 20 mm and lesions presented as nodules, with no significant difference between 2D and SM[27].

In Brazil, we have few published data regarding the performance of tomosynthesis. In the private clinic data obtained by one of the authors (Bauab SP) from July 2, 2012 to August 31, 2012, which included 1,220 women aged 40-83 years, submitted to tomosynthesis (COMBO mode or 2D complementary tomosynthesis), 12 cases of invasive cancer were found in asymptomatic patients. Tomosynthesis showed the lesion better in 9 cases, and in 3 cases the lesion was detected only by tomosynthesis, resulting in a 33% increase in the diagnosis of cancer in asymptomatic women.

Data from another private clinic (Aguillar VLN), included 4,314 women - 82% between 40 and 69 years and 58% with dense breasts (ACR C or D) - from September 2011 to August 2014, who were submitted to COMBO mode tomosynthesis, two views for each modality. Twenty-one carcinomas (10 *in situ* and 11 invasive) were detected by 2D and 27 carcinomas (10 *in situ* and 17 invasive) were detected by 3D. The six invasive carcinomas detected by tomosynthesis-only, were all seen as architectural distortions and stage I, positive hormone receptors and only one SL positive, with micrometastases. The cancer detection rate with 2D was 4.87 carcinomas/thousand exams; and with 3D, 6.26 carcinomas/thousand exams, representing an absolute increase of 1.4 carcinomas/thousand exams and a relative increase of 28.6%. Invasive detection rate with 2D was 2.54 invasive carcinomas/thousand exams, whereas with 3D it was 3.94 invasive carcinomas/thousand exams, representing a relative increase of 54%.

Regarding the characteristics of the carcinomas detected only by tomosynthesis, similar results were demonstrated in the prospective and retrospective studies. There was a significant increase in the detection of invasive carcinomas with tomosynthesis: 40% in the study by Oslo[13], 49% in STORM 1[21], 41% in Malmö[23] and 45% in the American multicenter retrospective study[26]. Forty to forty-eigth had histological grade 2 or 3 and 76 to 90% presented with negative sentinel lymph node[14,23]. There was no significant increase in carcinoma *in situ*.

Another important finding were the preliminary results from Malmo Trial (MBTST), presented at the European Congress of Radiology (Vienna, 2017), including all participants of the study (15.000 twomen). Among the additional invasive carcinomas detected only by tomosynthesis, 58% were ductal and 26% were lobular, whereas in the group detected by 2D, only 17% were lobular. The authors suggest that tomosynthesis may have a higher sensitivity for detection of lobular carcinomas compared to 2D mammography (Table 2, Figures 14 and 15)[28].

Diagnostic tomosynthesis:

In diagnostic cases, tomosynthesis increases accuracy, reduces the number of additional mammographic incidences[29,30] and reduces the probability of category 3 lesions of ACR BI-RADS, mainly focal asymmetries[31-33]. Tomosynthesis plays an important role in the confirmation of cutaneous lesions, in the evaluation of findings in a single incidence (mainly asymmetries) and in palpable lesions. It reduces need for additional mammographic incidences, with a faster and cheaper workflow and lower radiation dose[34,35].

Cutaneous lesions such as warts, sebaceous cysts or calcifications are observed in the more superficial slices of tomosynthesis, in which dermis and cutaneous pores are also visualized, confirming the superficial location of these lesions. Tomosynthesis does not require tangential incidences[34].

For asymmetries, tomosynthesis proves that most of the findings observed in only one incidence represent normal breast overlapping with no need for additional projections[33].

For palpable lesions, tomosynthesis, together with ultrasonography, in general, are diagnostic, with no need for extra views, such as spot compression or roll angle incidences (Figure 16)[34,35].

In the presence of a nodule of circumscribed margins evidenced in the tomosynthesis, an ultrasonography should be used to characterize its cystic or solid nature (Figures 17 and 18).

Table 2. Carcinomas detected only by tomosynthesis.

Study	Detection rate/thousand (2D)	Detection rate/thousand (tomosynthesis)	Relative carcinoma increase	Relative invasive carcinoma increase	Histological grade 2 or 3	Negative sentinela lymph node
STORM1[21]	5.3	8.1	53%	49%		60%
OTST[17]	6.1	8.0	27%	45%	40%	76%
MBTST[23]	6.3	8.9	43%	42%	48%	90%
STORM2[22]	6.3	8.8	35%		69%	86%
	6.3	8.8	40%			
Multicenter United State[26]	4.2	5.4	29%	41%		

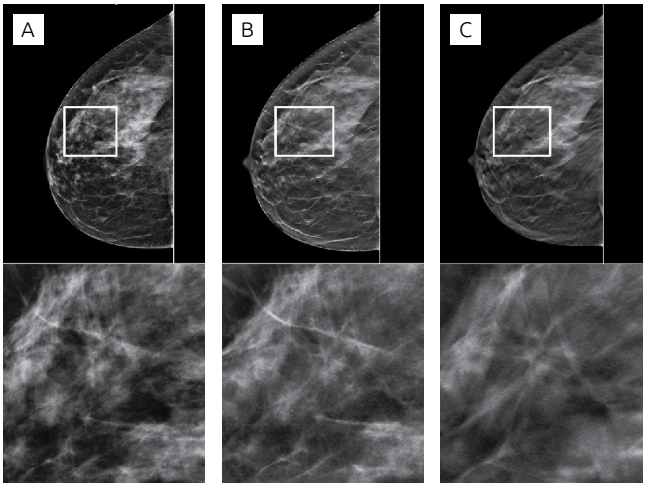


Figure 14. Focal architecture distortion is not evidenced in 2D (A) nor in synthesized 2D mammography (B). It is characterized in tomosynthesis (C).

Breast density and tomosynthesis

A multicentric study specifically developed to correlate the efficiency of tomosynthesis in different mammographic patterns of ACR BI-RADS found that tomosynthesis is better than 2D DM alone in dense or non-dense breasts, justifying its use in any mammographic pattern. However, the subgroup analysis showed that the sensitivity of tomosynthesis is lower in extremely dense breasts (ACR D) than in the other groups due to lack of adipose tissue in the breast, necessary for lesions detection. (Table 3)[36].

Preliminary results with 15,000 participants from the Swedish prospective study by Malmö[23] show that tomosynthesis increases cancer detection in all mammographic patterns. Of the tumors detected only by tomosynthesis, 46% were in women with non-dense breasts (ACR A and B) and 54% in dense breasts (ACR C and D).

In daily use, the greatest gain in tomosynthesis screening is observed in women with scattered fibroglandular densities (ACR B)

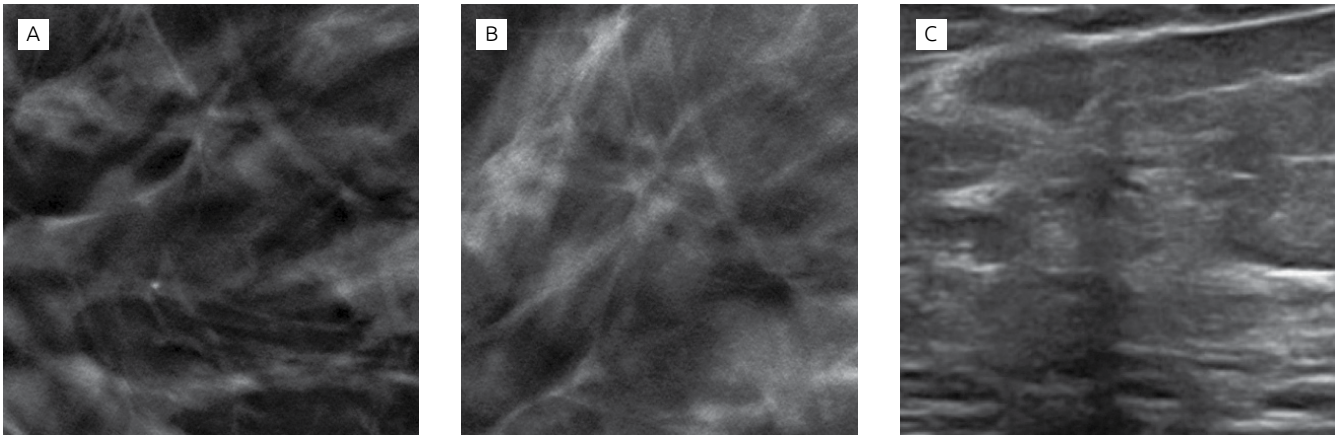


Figure 15. Focal architecture distortion only in oblique mediolateral (A) and craniocaudal (B) incidences in tomosynthesis (B). It is characterized in ultrasound (C). Histology: invasive lobular carcinoma grade I.

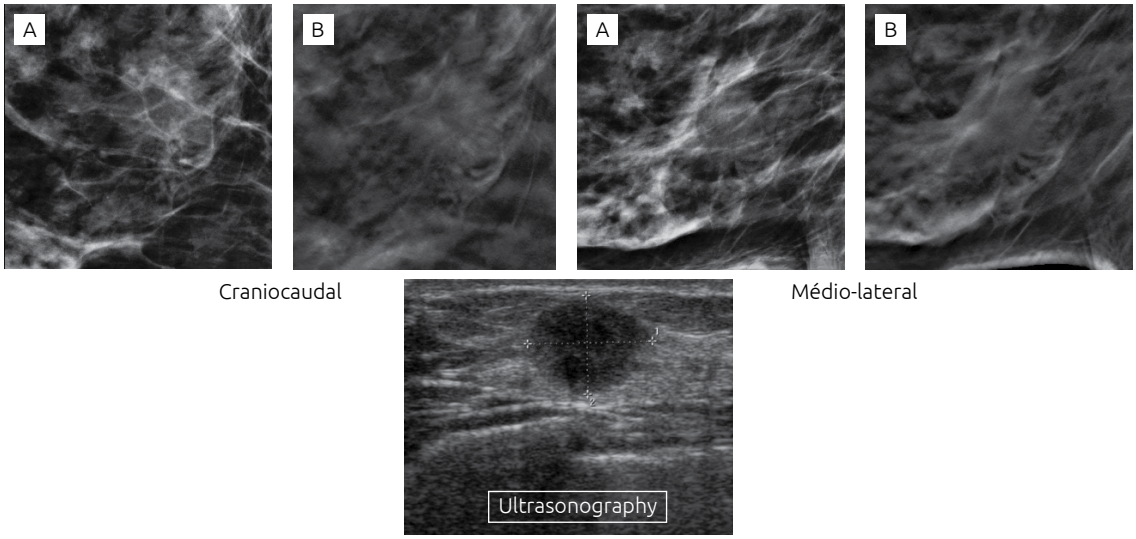
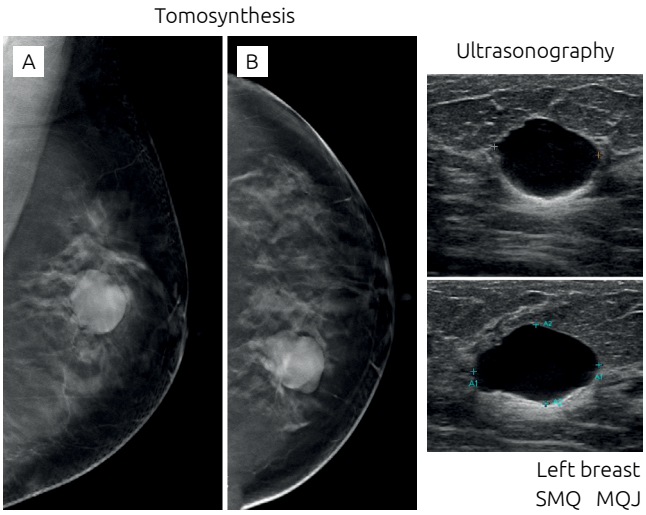
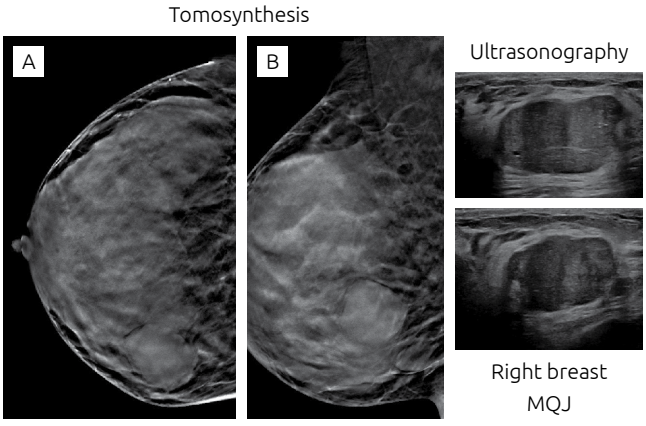


Figure 16. Palpable nodule to the right in heterogeneous dense breast, not observed in 2D (A) is presented in tomosynthesis (B) with spiculated margins. Ultrasonography shows a 1.4 cm nodule . Histopathology: invasive carcinoma g2.



SMQ: superomedial quadrant; MQJ: medial quadrant junction.

Figure 17. Heterogeneously dense breast. Tomosynthesis shows circumscribed margins of the lesion: (A) mediolateral incidence; (B) craniocaudal incidence. Ultrasonography shows cyst.



MQJ: medial quadrante junction.

Figure 18. Heterogeneously dense breast. Tomosynthesis shows circumscribed margins of the lesion: (A) mediolateral incidence; (B) craniocaudal incidence. Ultrasonography characterizes the solid nature of the lesion. Histology: fibroadenoma.

and heterogeneously dense breasts (ACR C), which represent the majority of breast density patterns. In women with extremely dense breasts (ACR D), complementary ultrasonography will continue to play an important role due to the lower sensitivity of tomosynthesis in this group (Figure 19)[33].

Detection of calcifications in tomosynthesis

Although there is no doubt that tomosynthesis is superior to 2D in the detection and characterization of noncalcified lesions (nodules, asymmetries and distortions), there are still questions related to grouped calcifications. Some studies showed that tomosynthesis is at least equal to 2D in detecting microcalcifications[37,38]. However, the detection of clusters of small and faint calcifications can be a challenge to be perceived in tomosynthesis for several reasons:

1. The low radiation dose in the raw images can reduce reconstructed images' spatial resolution;
2. Movement of the patient during the acquisition of the tomosynthesis or the 2D image;
3. Tomosynthesis slices have parallel reconstruction to the detector, while suspicious microcalcifications have radial distribution in the breast. Therefore, grouped calcifications with linear or segmental distribution will be visualized in more than one slice of tomosynthesis, which makes it difficult to analyze its morphology and distribution. The addition of several 1-mm slices in a single image (slab) facilitates the visualization of the whole group although with loss of spatial resolution and bigger impact in small particles.

SM increases the brightness and contrast of calcifications and can improve their perception and characterization when combined with tomosynthesis. However, the detection of clustered calcifications in tomosynthesis or SM does not exclude the need for extra views with magnification spot compression amplified in both incidences (craniocaudal and 90 degrees mediolateral), essential for the characterization of their morphology and distribution and recommendation of management (Figure 20).

Table 3. Breast density and tomosynthesis.

	Adipose		Sparse densities		Heterogeneous density		Extremely dense		Not dense		Dense	
	2D	3D	2D	3D	2D	3D	2D	3D	2D	3D	2D	3D
Recall/thousand screenings	57	55	97	84	128	110	114	98	90	79	127	109
Cancer/thousand screenings	3.2	4.2	4.4	5.3	4.5	6.1	3.8	3.9	4.2	5.1	4.5	5.8
Invasive câncer/ thousand screenings	2.3	3.5	3.2	4.1	3.0	4.5	1.9	2.6	3.0	4.0	2.9	4.2
Positive predictive value by recall	6.2	8.4	4.9	6.9	3.8	5.9	3.7	4.3	5.1	7.1	6.2	8.4

Source: adapted[36].

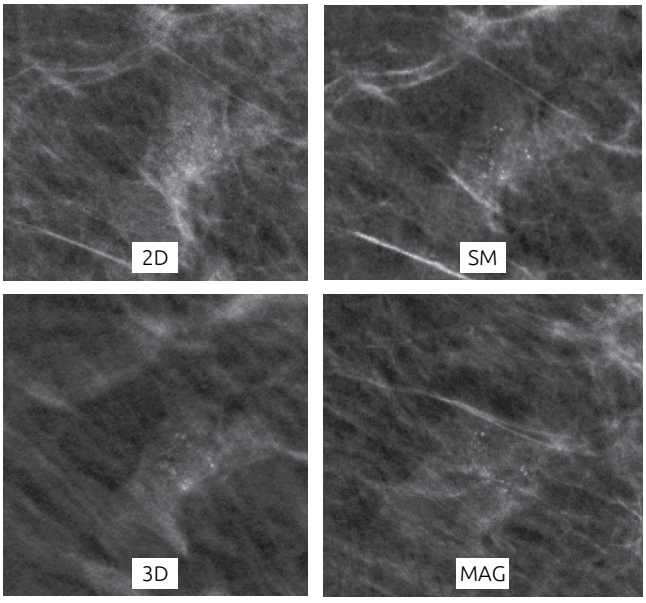
In some cases, tomosynthesis may add to the final mammographic diagnosis by detecting radiographic changes associated with clustered calcifications, such as focal architectural distortion, asymmetries or nodules (Figure 21).

Management of lesions detected only in tomosynthesis

Some lesions are detected only in tomosynthesis (hidden in the 2D), mainly spiculated nodes and architectural distortions, due to better resolution of spicules in tomosynthesis. In cases where the change is only suspected, selective compression can be performed to confirm the finding[33].

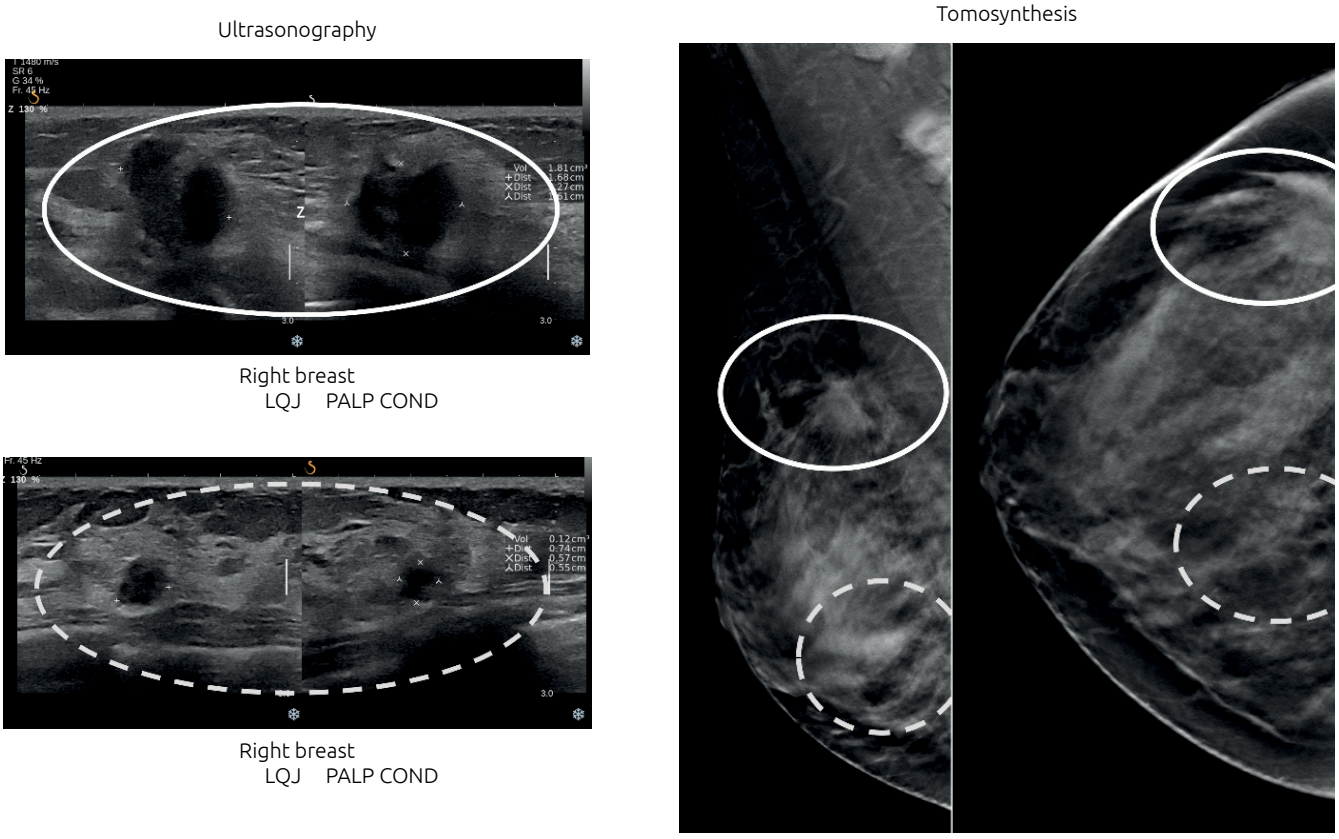
Tomosynthesis facilitates the localization of a lesion in the breast, through the lateral bar shown in its slices: for example, in the craniocaudal incidence, the bar demonstrates whether the lesion is in the lower or upper quadrant and, in the mediolateral incidence, it demonstrates whether the lesion is lateral or medial. The sidebar also guides the location of the lesion on the second look examination and helps when the image is only seen in one incidence[39].

Most of the changes observed only in tomosynthesis are also characterized by second look ultrasound which allows for



MAG: magnified radiography.

Figure 20. Calcifications in 2D synthesized mammography (SM) presents better conspicuity than in 2D. Although calcifications can be detected in tomosynthesis (3D), the magnified spot compression (MAG) better characterizes their shape and distribution. Histopathology: ductal carcinoma *in situ*.



SMQ: superomedial quadrant; PALP COND: palpable density; LQJ: lower quadrant junction.

Figure 19. In breasts with extremely dense pattern (D pattern), even in tomosynthesis the lesion may be obscured by dense tissue (dashed line). Ultrasonography is able to detect these lesions. The largest and most peripheral lesion (continuous line) was detected in both methods. Histopathology: multicentric invasive ductal carcinoma.

a percutaneous biopsy by this method. In cases where the lesion is not evident on ultrasonography, magnetic resonance imaging (MRI) is an option, if it enhances. Percutaneous vacuum biopsy may be guided by this modality. In cases where the lesion is not characterized on ultrasonography or does not show MRI enhancement or MRI is not available, a tomosynthesis-guided percutaneous biopsy may be performed, when available, on the biopsy prone table or in the biopsy equipment coupled to the tomosynthesis equipment. If the tomosynthesis biopsy equipment is not available, the tomosynthesis-guided preoperative location can be performed through tomosynthesis equipment : the procedure is performed similarly to the biplanar preoperative location (Figures 22 and 23)[40].

Among the findings seen only in tomosynthesis, architectural focal distortion is the most frequent finding and may be associated to several pathologies (Figure 24). However, it has a high positive predictive value (PPV) for malignancy. Recent studies, with retrospective analysis of findings detected only by tomosynthesis, show PPV from 21 to 53%. The work of Partyka et al.[41], a retrospective analysis of 9,982 tomosynthesis

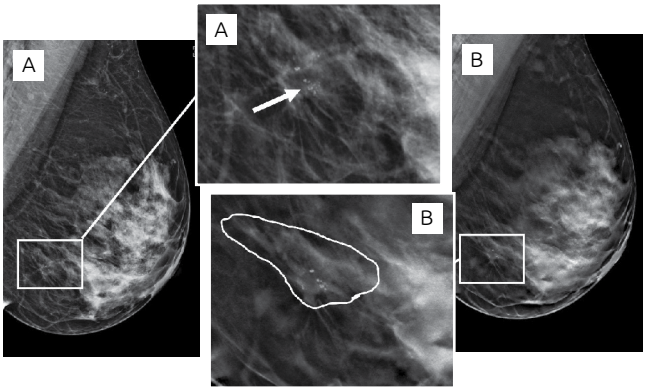


Figure 21. Conventional digital mammography (A) shows suspicious calcifications (arrows) and tomosynthesis (B) shows architectural distortion as an additional finding to microcalcifications, which may represent an invasive component of the lesion.

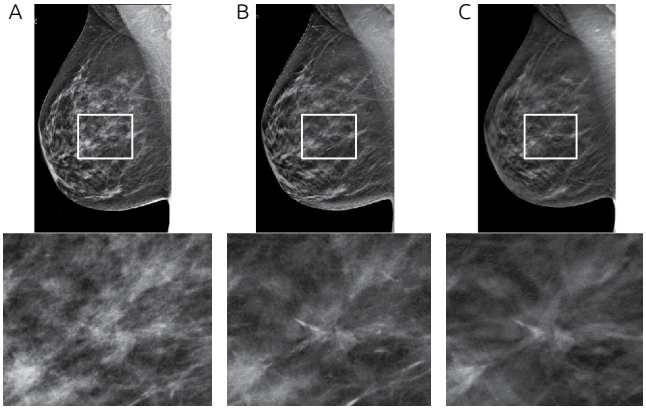


Figure 22. Focal architecture distortion is not evidenced in 2D (A). In mediolateral incidence, it is characterized in SM (B) and in tomosynthesis (C). Ultrasound and MRI not showing this finding.

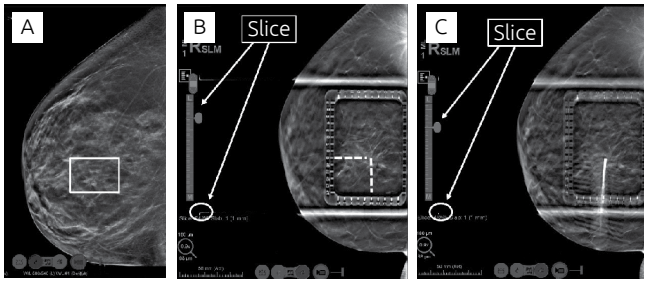


Figure 23. Preoperative location in mediolateral incidence, assisted by tomosynthesis, of the focal architecture distortion not seen in ultrasound and MRI (Figure 23). The positioning of the needle on axes x and y (dashed line) is provided by synthesized mammography (A) and depth (Z axis) by tomosynthesis (B). Positioning of the needle confirmed by tomosynthesis slice (C).

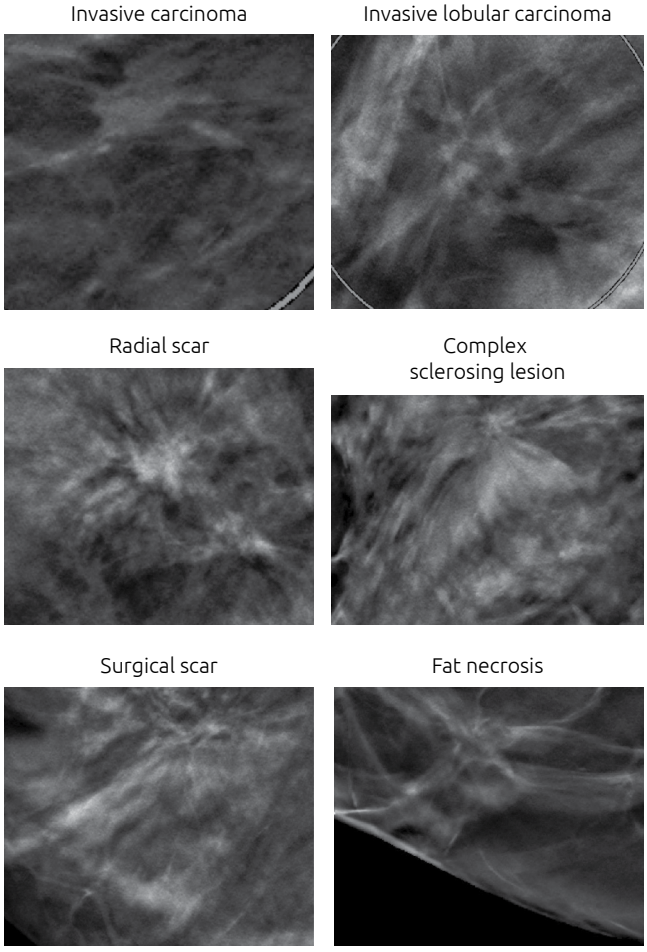


Figure 24. Architectural distortion may be associated with several diseases, requiring a histological study

examinations, found 26 cases of architectural distortion, of which 19 (73%) were detected only in tomosynthesis, with a PPV of 21% (4/19). Ray et al.[42] retrospectively analyzed 19 lesions detected by tomosynthesis only (14 cases of architectural distortion and 5 of spiculated masses), of which 10 were malignant (5 invasive ductal carcinomas and 3 invasive lobular carcinomas), with PPV of 53%.

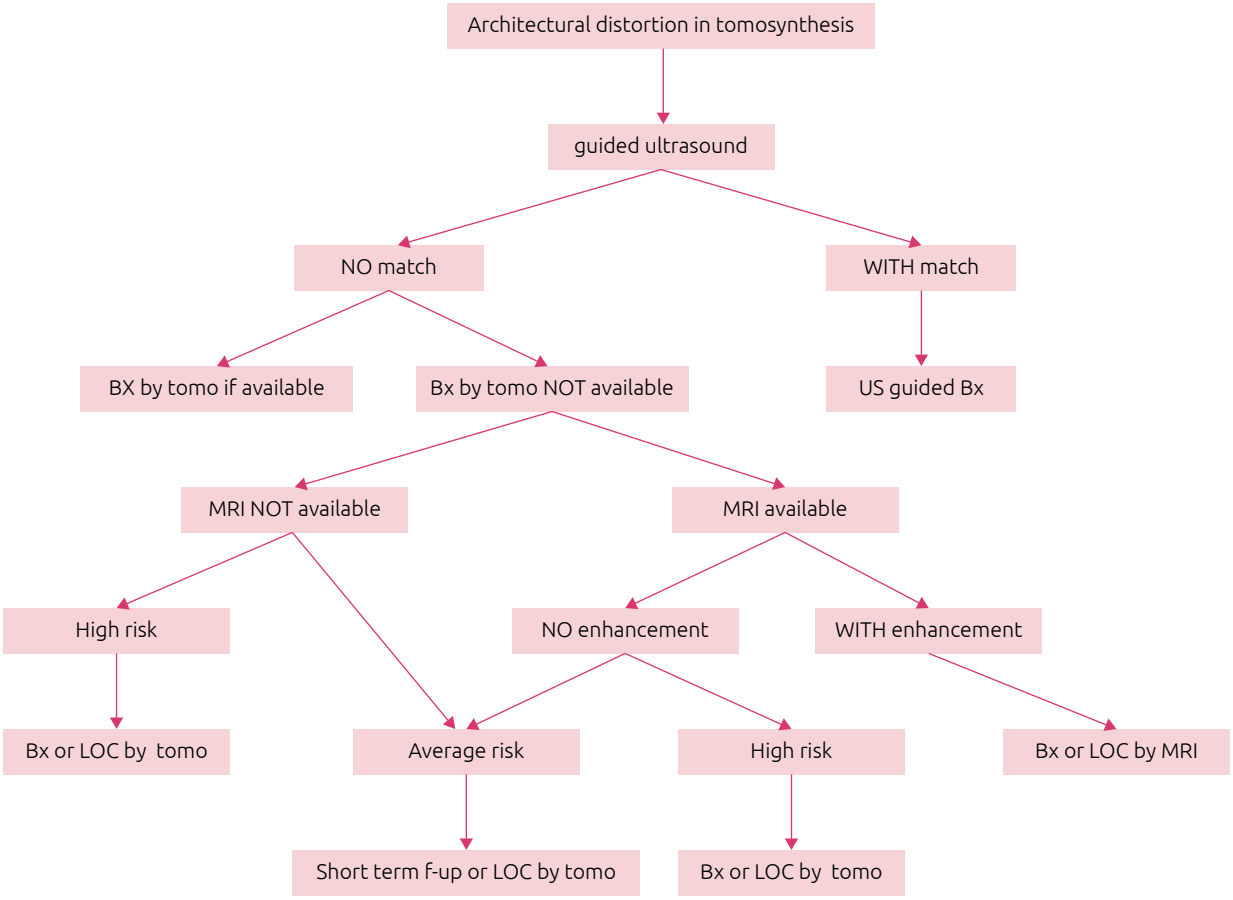
Risk factors for breast cancer should be taken into account, and biopsy may be indicated instead of follow-up for high-risk patients. A modified algorithm by Durand et al.[39] is proposed, considering the risk of breast cancer and the availability or not of MRI (Figure 25).

Future studies are needed to determine the likelihood of malignancy in architectural distortions detected only in tomosynthesis, without characterization in ultrasound or in MRI, to establish new protocols related to these lesions.

Could tomosynthesis replace ultrasound?

Dense breasts reduce mammography's sensitivity, being recommended, in those cases, complementary tracing with other methods. Numerous studies have found that ultrasonography, as well as tomosynthesis, detect small invasive cancers, not seen on mammography, even retrospectively, in women with dense breasts. Tomosynthesis has the advantage of being only one exam (an improved mammography), with high PPV, but with a higher implementation and maintenance cost. Ultrasonography is an additional exam, with low cost and widely available, without radiation addition, though it has low predictive value and needs an experienced radiologist to be performed. There is little information on which exam to choose, as a complement to 2D, in women with dense breasts: only ultrasonography, only tomosynthesis or both?

Tagliafico et al.[43] published a multicenter study with 3,231 women, mean age of 51 years, in which tomosynthesis and ultrasonography were performed, with independent interpretation, in women with dense breasts and negative mammography. The study observed the detection of 24 additional cancers in relation to digital mammography, with 23 invasive ones. The detection rate was 4/1000 with tomosynthesis and 7.1/1000 with ultrasonography, with a similar recall rate in both methods. The study concludes that ultrasound detects more cancers than tomosynthesis in women with dense breasts.



Bx: biopsy; tomo: tomosynthesis; US: ultrasonography; MRI: magnetic resonance imaging; LOC: preoperative location; F-up: follow-up.

Figure 25. Algorithm for management in architectural distortion evidenced in tomosynthesis.

Therefore, tomosynthesis does not exempt complementary ultrasonography in dense breast breasts.

An important finding was the detection, through tomosynthesis, of more than 50% of the additional cancers found, showing that potentially, tomosynthesis could replace 2D as the primary cancer screening method in dense breasts. Unlike ultrasonography, tomosynthesis increases cancer detection without increasing the rate of false positives, which is the most critical point in relation to ultrasound screening.

We must remember that the results published are preliminary and that this study needs to be reproduced in other centers. In addition, it was the first shift with tomosynthesis in this group (little experience of the authors with tomosynthesis), while most of the ultrasound examinations were incident and performed with professionals experienced in the method (Table 4)[43].

In clinical practice, it can be observed that tomosynthesis does not completely replace ultrasound. In very dense and heterogeneously dense breasts, complementary ultrasonography should still be recommended, since it is possible to detect small lesions on ultrasound, not characterized in tomosynthesis, especially in breasts with extremely dense pattern, in which there is insufficient adipose tissue to make contrast in tomosynthesis slices (Figure 19).

Table 4. Carcinomas detected only by tomosynthesis.

	Positive ultrasound	Negative ultrasound	Total n (%)
Positive tomography	12	1	13 (54.2)
Negative tomography	11	0	11 (45.8)
Total n (%)	23 (95.8)	8.9 (4.2)	

Source: adapted[43].

Interval carcinomas and tomosynthesis screening

The rate of interval cancers (ICR) after introduction of tomosynthesis into screening still needs to be investigated. Evidence that tomosynthesis (combined with 2D) reduces the rate of interval carcinoma is still limited .Skaane et al.[44] didn't show reduction in the ICR after the first year of introduction of tomosynthesis: 2,0 IC/1000 with 2D and 2,1 IC/1000 with 2D+3D. On the other hand, a study from Pensylvannia [45] which analyzed the results of three years follow-up with tomosynthesis, demonstrated a small reduction in ICR with tomosynthesis (0,7/1000 with 2D versus 0,5/1000 with tomo). However, these are individual studies with small number of patients and more data is needed.

CONCLUSION

Tomosynthesis (3D mammography) is a new mammographic technique that increases sensitivity and specificity when combined to 2D mammography (conventional or synthesized)

In screening, tomosynthesis has a positive impact because increases detection of small , low grade, RH positive and LN negative invasive cancers and reduces unnecessary recalls or need for additional mammographic incidences.

In diagnostic cases, the technique increases diagnostic accuracy by allowing for a better characterization and location of the lesions, making the conventional diagnostic approach unnecessary, with reduction of patients' anxiety and lower financial cost.

With the development of SM, reconstructed from tomosynthesis to replace conventional 2D imaging, the problem of increased total radiation dose — considered an obstacle to this method in screening — has been solved.

Future studies of interval cancer incidence and cost-benefit analysis of this technology should provide new data for implementation of tomosynthesis in large-scale breast cancer screening.

REFERENCES

1. Skaane P, Gullien R, Bjorndal H, Eben EB, Eksebh UH, Jahr G, et al. Digital breast tomosynthesis (DBT): initial experience in a clinical setting. Acta Radiol. 2012;53(5):524-9. https://doi.org/10.1258/ar.2012.120062
2. Hardesty LA. Issues to Consider Before Implementing Digital Breast Tomosynthesis Into a Breast Imaging Practice. Am J Roentgenol. 2015;204:681-4. https://doi.org/10.2214/AJR.14.13094
3. Kopans DB. Digital breast tomosynthesis from concept to clinical care. Am J Roentgenol. 2014;202:299-308. https://doi.org/10.2214/AJR.13.11520
4. Vedantham S, Karellas A, Vizayaraghavan GP, Kopans DB. Digital Breast Tomosynthesis: state of the art. Radiology. 2015;272(3):663-84. https://doi.org/10.1148/radiol.2015141303
5. Sechopoulos I. A review of breast tomosynthesis. Part I. The image acquisition process. Med Phys. 2013;40:014301. https://doi.org/10.1118/1.4770279
6. Sechopoulos I. A review of breast tomosynthesis. Part II. Image reconstruction, processing and analysis, and advanced applications. Med Phys. 2013;40:14302. https://doi.org/10.1118/1.4770281
7. Svahn TM, Houssami N, Sechopoulos I, Mattsson S. Review of radiation dose estimates in digital breast tomosynthesis relative to those in two-view full-field digital mammography. Breast. 2015;24(2):93-9. https://doi.org/10.1016/j.breast.2014.12.002

8. Skaane P, Bandos AI, Eben EB, Jebsen IN, Krager M, Haakenaasen U, et al. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: comparison with digital breast tomosynthesis with full-field digital mammographic images. Radiology. 2014;271(3):655-63. https://doi.org/10.1148/radiol.13131391
9. Zuley ML, Guo B, Catullo VJ, Chough DM, Kelly AE, Lu AH, et al. Comparison of two-dimensional synthesized mammograms versus original digital mammograms alone and in combination with tomosynthesis images. Radiology. 2014;271(3):664-71. https://doi.org/10.1148/radiol.13131530
10. Zuckerman SP, Conant EF, Keller BM, Maidment ADA, Barufaldi B, Weinstein SP, et al. Implementation of synthesized two-dimensional mammography in a population based digital breat tomosynthesis screening program. Radiology. 2016;281(3):730-6. https://doi.org/10.1148/radiol.2016160366
11. Wallis MG, Moa E, Zanca F, Leifland K, Danielsson M. Two-view and single-view tomosynthesis versus full-field digital mammography: high resolution X-ray imaging observer study. Radiology. 2012;262(3):788-96. https://doi.org/10.1148/radiol.11103514
12. Rafferty EA, Park JM, Philpotts LE, Poplack SP, Sumkin JH, Halpern EF, et al. Diagnostic accuracy and recall rates for digital mammography and digital mammography combined with one-view and two-view tomosynthesis: results of an enriched reader study. Am J Roentgenol. 2014;202(2):273-81. https://doi.org/10.2214/AJR.13.11240
13. Beck N, Butler R, Durand M, Andrejeva, Hooley R, Horvath L, et al. One-View Versus Two-View Tomosynthesis: A Comparison of Breast Cancer Visibility in the Mediolateral Oblique and Craniocaudal Views. In: ARRS; 2013. Scientific Session 27, Breast Imaging. 2013.
14. Skaane P, Bandos A, Gullien R, Eben EB, Ekseth U, Haakenaasen U, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology. 2013;267(1):47-56. https://doi.org/10.1148/radiol.12121373
15. Rafferty EA., Belfer AJ. Tomosynthesis & synthesized 2-D imaging part II: the evolution of mammography. Applied Radiology Experts Forum Webinars. October, 2013.
16. Dang PA, Free PE, Humphrey KL, Halpern EF, Rafferty EA. Addition of tomosynthesis to conventional diagnostic mammography: effect on image interpretation time of screening examinations. Radiology. 2014;270(1):49-56. https://doi.org/10.1148/radiol.13130765
17. Houssami N, Bernardi D, Pellegrini M, Valentini M, Fanto C, Ostilliò L, et al. Breast cancer detection using single-reading for breast tomosynthesis (3 D mammography) compared to double reading of 2 D mammography: evidence from a population-based trial. Cancer Epidemiol. 2017;47:94-9. https://doi.org/10.1016/j.canep.2017.01.008
18. Haas BM, Kalra V, Geisel J, Raghu M, Durand M, Philpotts LE. Comparison of tomosynthesis plus digital mammography and digital mammography alone for breast cancer screening. Radiology. 2013;269(3):694-700. https://doi.org/10.1148/radiol.13130307
19. Rose SL, Tidwell AL, Bujnoch LJ, Kushwaha AC, Nordmann AS, Sexton R Jr. Implementation of breast tomosynthesis in a routine screening practice: an observational study. Am J Roentgenol. 2013;200(6):1401-8. https://doi.org/10.2214/AJR.12.9672
20. Rafferty EA, Park JM, Philpotts LE, Poplack SP, Sumkin JH, Halpern EF, et al. Assessing radiologist performance using combined digital mammography and breast tomosynthesis compared with digital mammography alone: results of a multicenter, multireader trial. Radiology. 2013;266(1):104-13. https://doi.org/10.1148/radiol.12120674
21. Ciatto S, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. Lancet Oncol. 2013:14(7):583-9. https://doi.org/10.1016/S1470-2045(13)70134-7
22. Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fantò C, Ostillio L, et al. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM 2): a population-based prospective study. Lancet Oncol. 2016;17(8):1105-13. https://doi.org/10.1016/S1470-2045(16)30101-2
23. Lang K, Andersson I, Rosso A, Tingberg A, Timberg P, Zackrisson S. Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: results from the Malmo Breast Tomosynthesis Screening Trial, a population-based study. Eur Radiol. 2016;26:184-90. https://doi.org/10.1007/s00330-015-3803-3
24. Houssami N, Skaane P. Overview of the evidence on digital breast tomosynthesis in breast cancer detection. Breast. 2013;22(2):101-8. https://doi.org/10.1016/j.breast.2013.01.017
25. McCarthy AM, Kontos D, Synnestvedt M, Tan KS, Heitjan DF, Schnall M, at al. Screening Outcomes Following Implementation of Digital Breast Tomosynthesis in a General Population Screening Program. J Natl Cancer Inst. 2014;106(11):1-7. https://doi.org/10.1093/jnci/dju316
26. Friedewald SM, Rafferty EA, Rose SL, Durand M, Plecha DM, Greenberg JS, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. JAMA. 2014;311(24):2499-507. https://doi.org/10.1001/jama.2014.6095
27. Gilbert FJ, Tucker L, Gillan MG, Willsher P, Cooke J, Duncan KA, et al. Accuracy of Digital Breast Tomosynthesis for depicting breast cancer subgroups in a UK retrospective reading study (TOMMY Trial). Radiology. 2015;277(3):697-706. https://doi.org/10.1148/radiol.2015142566
28. Lang K, Experiences from the Malmö breast tomosynthesis screening trial Presented at the ECR Annual Meeting, Vienna 2017, Scientific Session Breast tomosynthesis symposium: Is digital breast tomosynthesis ready for mammo screening? In: ECR Annual Meeting, Vienna, 2017. 2017.
29. Noroozian M, Hadjiiski L, Rahnama-Moghadam S, Klein KA, Jeffries DO, Pinsky RW, et al. Digital Breast Tomosynthesis Is Comparable to Mammographic Spot Views for Mass Characterization. Radiology. 2012;262(1):61-8. https://doi.org/10.1148/radiol.11101763
30. Brandt KR, Craig DA, Hoskins TL, Henrichsen TL, Bendel EC, Brandt SR, et al. Can digital breast tomosynthesis replace conventional diagnostic mammography views for screening recalls without calcifications? A comparison study in a simulated clinical setting. Am J Roentgenol. 2013;200(2):291-8. https://doi.org/10.2214/AJR.12.8881

31. Durand MA, Haas BM, Yao X, Geisel JL, Raghu M, Hooley RJ, et al. Early clinical experience with digital breast tomosynthesis for screening mammography. Radiology. 2015;274(1):85-92. https://doi.org/10.1148/radiol.14131319

32. Lourenço AP, Barry-Brooks M, Baird GL, Tuttle A, Mainiero MB. Changes in recall type and patient treatment following implementation of screening digital breast tomosynthesis. Radiology. 2015;274:337-42. https://doi.org/10.1148/radiol.14140317

33. Hooley RJ, Durand MA, Philpotts LE. Advances in Digital Breast Tomosynthesis. Am J Roentgenol. 2017;208:256-66. https://doi.org/10.2214/AJR.16.17127

34. Chong A, McDonald ES, Weinstein S, Roth S, Tobey J, Conant EF. Digital breast tomosynthesis: challenging the traditional workflow dogma: poster. In: Radiological Society of North America, 2016. Scientific Assembly and Annual Meeting [Internet]. 2016. Disponível em: archive.rsna.org/2016/16004083.html

35. Conant EF, Beaber EF, Sprague BL, Herschorn SD, Weaver DL, Onega T, et al. Breast cancer screening using tomosynthesis. Breast Cancer Res Treat. 2016;156:109-16. https://doi.org/10.1007/s10549-016-3695-1

36. Rafferty EA, Durand MA, Conant EF, Copit DS, Friedewald SM, Plecha DM, et al. Breast cancer screening with tomosynthesis and Digital Mammography in Dense and Non-dense Breasts. JAMA. 2016;315(16):1784-6. https://doi.org/10.1001/jama.2016.1708

37. Spangler ML, Zuley ML, Sumkin JH, Abrams G, Ganott MA, Hakim C, et al. Detection and classification of calcifications on digital breast tomosynthesis and 2D digital mammography: a comparison. Am J Roentgenol. 2011:196(2):320-4. https://doi.org/10.2214/AJR.10.4656

38. Kopans D, Gavenonis S, Halpern E, Moore R. Calcifications in the breast and digital breast tomosynthesis. Breast J. 2011;17:638-44. https://doi.org/10.1111/j.1524-4741.2011.01152.x

39. Durand MA, Wang S, Hooley RJ, Raghu M, Philpotts LE. Tomosynthesis-detected Architectural Distortion: Management Algorithm with Radiologic-Pathologic Correlation, RadioGraphics. 2016;36:311-21. https://doi.org/10.1148/rg.2016150093

40. Freer PE, Niell B, Rafferty EA. Preoperative Tomosynthesis-guided needle localization of Mammographically and sonographically Occult Breast lesions, Radiology. 2015;275(2):377-83. https://doi.org/10.1148/radiol.14140515

41. Partyka L, Lourenco AP, Mainiero MB. Detection of mammographically occult architectural distortion on digital breast tomosynthesis screening: initial clinical experience. Am J Roentgenol. 2014;203(1):216-22. https://doi.org/10.2214/AJR.13.11047

42. Ray KM, Turner E, Sickles E, Joe BN. Suspicious findings at digital breast tomosynthesis occult to conventional digital mammography: imaging features and pathological findings. Breast J. 2015;21(5):538-42. https://doi.org/10.1111/tbj.12446

43. Tagliafico AS, Calabrese M, Mariscotti G, Durando M, Tosto S, Monetti F, et al. Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts: Interim Report of a Prospective Comparative Trial. J Clin Oncol. 2016;34(16):1882-88. https://doi.org/10.1200/JCO.2015.63.4147

44. Skaane P, Sebuodegard S, Gur D, Gullien R, Hofvind SS. Screen-detected and interval cancers before, during, and after implementation of digital breast tomosynthesis in a population-based mammography screening program [Internet]. In: Radiological Society of North America, 2015. Scientific Assembly and Annual Meeting. 2015. Disponível em: archive.rsna.org/2015/15017637.html

45. McDonald ES, Oustimov A, Weinstein SP, Synnestvedt MB, Schnall M, Conant EF. Effectiveness of Digital Breast Tomosynthesis Compared With Digital Mammography Outcomes Analysis from 3 Years of Breast Cancer Screening JAMA Oncol. 2016;2(6):737-43. https://doi.org/10.1001/jamaoncol.2015.5536

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With authorship

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Theses and Dissertations

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