

# MASTOLOGY

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# MASTOLOGY

*Official Journal of the Brazilian Society of Mastology*

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## I INSTRUCTIONS TO AUTHORS

# ANAPLASIC LARGE CELLS LYMPHOMA ASSOCIATED WITH BREAST IMPLANTS

Linfoma anaplásico de grandes células associado a implantes mamários

Bernardo Nogueira Batista<sup>1\*</sup> 

**N**ews of a new lymphatic neoplasm associated with breast implants have worried, to varying degrees, breast surgeons around the world. Anaplastic Large Cells Lymphoma (ALCL) is a rare type of T-cell non-Hodgkin's disease that, when unrelated to breast implants, is preferentially manifested on the skin and has a good prognosis. In 10% of these cases, the disease may extend to lymph nodes and organs, with a less favorable prognosis<sup>1</sup>.

In 1997, the first report of an anaplastic T-cell lymphoma associated with a saline implant in a patient with prior augmentation mammoplasty was published in the USA<sup>2</sup>. Twenty years later, a little more than a two hundred cases have been described and Breast Implant Associated ALCL (BIA-ALCL) has been recognized as an independent entity in the classification of lymphoid neoplasms of the World Health Organization (WHO)<sup>3</sup>.

The impact this new entity will have on the public is not yet clear, but it has become a growing concern for the modern practice of breast surgery. To date, little is known about the pathology, given the rarity of its occurrence. It is now estimated that the prevalence of the disease is 1 case in every 30,000 women with breast implants<sup>4</sup>. However, this number has increased rapidly as efforts by some regulatory agencies and medical societies abroad have intensified to standardize and centralize information. The National Comprehensive Cancer Network has recently published a consensus for identification and management of suspected cases<sup>5</sup>.

On average, the diagnosis of a BIA-ALCL occurs 10 years after implantation. The most frequent clinical presentation is that of a late seroma leading to an increase in breast volume. Any peri-implant seroma that occurs more than one year after placement of the prosthesis should be submitted to aspiration and anatomopathological and immunohistochemical studies. Pathologists should be informed about the clinical suspicion of BIA-ALCL and the specific tests required, as these are not routinely performed on breast specimens or on traditional lymphoma panels. In the collected fluid, ALK and flow cytometry for CD30 must be performed. BIA-ALCLs show abundant pleomorphic, CD30-positive and ALK-negative lymphocytes. It is important to emphasize that, in the presence of a late seroma, its benign presentation is still the most likely diagnosis. However, suspicion is very important, and, if confirmed, the patient will require additional testing before surgery and a multidisciplinary treatment. Inadequate treatment of a BIA-ALCL can have tragic consequences.

Any confirmed case should be discussed in a multidisciplinary group. The evidence about the need/efficiency of the different therapeutic options is still weak. It is recommended to perform a preoperative PET scan for further comparison during follow-up. Removal of the implant with total capsulectomy seems to be sufficient to treat BIA-ALCL in cases where the disease is restricted to the capsule (stage I). BIA-ALCLs have been reported in association with all types of textured implants. However, studies suggest that some manufacturers may present a higher risk than others<sup>6</sup>. No case has been confirmed in patients who have used only smooth implants.

Another form of presentation, present in about 15% of the cases, is the presence of a solid mass with or without an associated seroma. It is not yet clear whether these are different forms of the disease or parts of its spectrum, but mass presentation has been associated with worse prognoses. In these cases (stage II), in patients who have evidence of disease outside the breast (stages III and IV) and in cases where there is suspicion of incomplete resection of the disease, the association of chemotherapy and/or radiotherapy should be discussed. Other less frequent presentations were reported, demonstrating the importance of surveillance by those in contact with patients with breast implants.

Frequent follow-up of patients with a confirmed BIA-ALCL diagnosis should be maintained after treatment to confirm remission of the disease. When available, follow-up should include a PET scan every 6 months for 2 years. In the vast majority of cases, prognosis

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BIA-ALCL: Breast Implant Associated Anaplastic Large Cell Lymphoma

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is good. Follow-up data are still inconsistent to accurately determine disease-free survival and its specific mortality. Cases of recurrence and even some deaths have been reported.

The way the media and the general public will respond to information about the existence of a rare neoplasm associated with breast implants will greatly depend on our ability to transmit and, more importantly, to educate the population. The Brazilian breast implant market is the second largest in the world and one of the most complex, with devices from 12 different manufacturers being sold at present times. Informally, we have been informed of at least 11 confirmed cases, one of them in a patient with an augmentation mammoplasty in whom we treated an ALCL last year<sup>7</sup>. The patient is in remission and being followed up. All these cases have in common a more advanced presentation and/or improper handling at the time of the first manifestation. The system of pharmacovigilance of breast implants of the National Agency of Sanitary Surveillance has not registered any case so far.

These data reinforce the importance of a broad and clear discussion to raise awareness of the breast surgery community about this new entity. We will all be exposed to possible cases of BIA-ALCL in the near future and eventually we will be inquired about the risks associated with the use of breast implants.





## REFERENCES

1. Leberfinger AN, Behar BJ, Williams NC, Rakszawski KL, Potochny JD, Mackay DR, et al. Breast implant-associated anaplastic large cell lymphoma: a systematic review. *JAMA Surg*. 2017. DOI: 10.1001/jamasurg.2017.4026
2. Keech JA, Creech BJ. Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. *Plast Reconstr Surg*. 1997;100(2):554-5.
3. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-90. DOI: 10.1182/blood-2016-01-643569
4. Doren EL, Miranda RN, Selber JC, Garvey PB, Liu J, Medeiros LJ, et al. U.S. Epidemiology of breast implant-associated anaplastic large cell lymphoma. *Plast Reconstr Surg*. 2017;139(5):1042-50. DOI: 10.1097/PRS.0000000000003282
5. Clemens MW, Horwitz SM. NCCN consensus guidelines for the diagnosis and management of breast implant-associated anaplastic large cell lymphoma. *Aesthetic Surg J*. 2017;37(3):285-9. DOI: 10.1093/asj/sjw259
6. Loch-Wilkinson A, Beath KJ, Knight RJ, Wessels WL, Magnusson M, Papadopoulos T, et al. Breast implant-associated anaplastic large cell lymphoma in Australia and New Zealand: high-surface-area textured implants are associated with increased risk. *Plast Reconstr Surg*. 2017;140(4):645-54. DOI: 10.1097/PRS.0000000000003654
7. Batista BN, Garicochea B, Aguilar VL, Carvalho FM, Millan LS, Fraga MF, et al. Report of a case of anaplastic large cell lymphoma associated with a breast implant in a Brazilian patient. *Rev Bras Cir Plást*. 2017;32(3):445-9. DOI: 10.5935/2177-1235.2017RBCP0073



# CHRONOTYPE IN BREAST CANCER AND RELATION TO DESYNCHRONIZATION OF THE CIRCADIAN CYCLE

## O cronotipo no câncer de mama e sua relação com a dessincronização do ciclo circadiano

Natália Gomes Gebin<sup>1</sup>, Stephanie Elisabeth Schroff<sup>1</sup>, Wilmar José Manoel<sup>2</sup>, Deidimar Cássia Batista Abreu<sup>2</sup>, Fábio Silvestre Ataides<sup>1</sup> , Cesar Augusto Sam Tiago Vilanova-Costa<sup>3</sup> , Jacqueline Andréia Bernardes Leão-Cordeiro<sup>4</sup> , Antonio Márcio Teodoro Cordeiro Silva<sup>1,5\*</sup> 

### ABSTRACT

**Introduction:** The circadian cycle plays several roles at the organism functions and are important to the maintenance of health, when synchronized. Nowadays, one of the main risk factors for the change of the sleep-wake cycle in the population is the high exposure to light at night, consequently deregulating the circadian cycle, inhibiting the release of melatonin and favoring oncogenesis. **Objectives:** The aim of this study was to identify the possible associations between circadian rhythm's desynchronization and breast cancer. **Methods:** This is a descriptive cross-sectional study and two collection instruments were used in it: sociodemographic questionnaire and the Horne and Ostberg matutinal-vespertine questionnaire. They were applied in a group of 74 women in a highly complex oncology service. **Results:** To evaluate whether the discriminant factors such as night work and chronotype exerted some influence on the discriminated factor that is breast cancer,  $\chi^2$  test was applied showing that the characteristics among the groups were similar and so it was not possible to confirm that there is a relationship between them. **Conclusions:** More studies about the subject is needed.

**KEYWORDS:** Breast neoplasms; circadian rhythm; carcinogenesis; melatonin.

### RESUMO

**Introdução:** O ciclo circadiano desempenha vários papéis nas funções do organismo e é importante para a manutenção da saúde, quando sincronizado. Atualmente, um dos principais fatores de risco para a mudança do ciclo vigília-sono na população é a alta exposição à luz noturna, desregulando consequentemente o ciclo circadiano, inibindo a liberação de melatonina e favorecendo a oncogênese. **Objetivo:** O objetivo deste estudo foi identificar as possíveis associações entre dessincronização do ritmo circadiano e o câncer de mama. **Métodos:** Trata-se de um estudo descritivo de corte transversal em que foram utilizados dois instrumentos de coleta: um questionário sociodemográfico e o questionário matutino-vespertino de Horne e Ostberg. Os questionários foram aplicados a um grupo de 74 mulheres em um serviço de oncologia. **Resultados:** Para avaliar se os fatores discriminantes como o trabalho noturno e o cronotipo exerceram alguma influência sobre o fator discriminado, câncer de mama, foi aplicado o teste do  $\chi^2$ , que revelou semelhança entre as características dos grupos estudados. **Conclusões:** Mais estudos sobre o assunto são necessários de forma a se compreender melhor a possível relação entre o ciclo circadiano e a susceptibilidade ao desenvolvimento de neoplasias, especialmente o câncer de mama.

**PALAVRAS-CHAVE:** Câncer de mama; ritmo circadiano; carcinogênese; melatonina.

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## INTRODUCTION

Humans, in 24 hours per day, undergo biological processes controlled by the circadian cycle, known as biological clock, such as the regulation of sleep-wake cycles, body temperature, energy metabolism, cell cycle and hormonal secretion.<sup>1</sup> The timing of these processes is responsible for maintaining the individual's health. However, some internal and external factors can interfere with the regulation of this cycle, the main one being the artificial light, which increases the risk of developing certain diseases, such as breast cancer.<sup>2</sup>

The rhythmicity of the sleep-wake cycle varies depending on each individual's age, and thus the chronotype, which is the sleep-wake cycle associated with interindividual differences.<sup>3</sup> With these changes in sleep-wake cycle, there are also changes in the rhythm of temperature and nocturnal melatonin peaks in each of these phases, thus showing changes in the biological clock.<sup>4</sup>

The biological clock's core consists in genes that will generate and regulate the circadian rhythms within the cells throughout the individual's body.<sup>5</sup> These genes belong to two families: Period and Cryptochrome, and are subdivided into Per1, Per2 and Per3, and Cry1 and Cry2.<sup>6</sup> They are activated by transcriptional factors, known as CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL1 (Brain-Muscle Arnt-Like protein 1), that will induce the expression of these genes.<sup>6,7</sup>

The circadian rhythm is capable of controlling the expression of cell cycle's genes. This control is carried out through the heterodimer CLOCK-BMAL1, acting on the cell cycle's genes, such as Wee1 (which acts in the G2-M transition); cMyc (the G0-G1 transition) and cyclin D1 (in the G1-S transition).<sup>1,8</sup> Due to this control, heterodimer can also function as a tumor suppressor at systemic, cellular and molecular levels.<sup>1</sup>

Nowadays, one of the main risk factors for the change of sleep-wake cycle is the high exposure to light at nighttime.<sup>7</sup> According to the theory "light at night," the increased use of electric light is related to the increased risk for breast cancer.<sup>9</sup> The mechanism is the reduction on melatonin production, thus increasing the release of estrogen by the ovary.<sup>10</sup> Some studies found that the risk of cancer rises as years of work or hours per week in night shift.<sup>9</sup>

One of the most important studies, the Nurse's Health Study, 1987, presented the risk association between night shift at work and breast cancer,<sup>10</sup> following nurses over a period of ten years. According to these studies, the risk for breast cancer had a moderate increase in women who have worked at night for an average of 14 years, while those who have worked for 30 years or more, showed a very high risk.<sup>7</sup>

Several studies also consider biological time as a tool to improve the treatment for certain diseases, which is known as chronotherapy. The circadian rhythm can also control some drugs' metabolism, varying its bioavailability. In experimental models, both the toxicity and efficacy of over thirty anti-cancer varied according to the period in which they were administered.<sup>1</sup>

In Brazil, breast cancer is the most common disease in women after nonmelanoma skin cancer and has a high mortality rate due to late diagnosis.<sup>11</sup> Therefore, it is necessary to know the various factors involved in its genesis. The aim of this study was to identify the possible relationship between changes in the circadian rhythm and breast cancer.

## METHODS

This is a descriptive cross-sectional study and two collection instruments were used in it: sociodemographic questionnaire and the Horne and Ostberg matutinal-vespertine questionnaire. These questionnaires were applied in a group of 74 women in a highly complex oncology service to treat breast cancer.

Both questionnaires were approved by the Ethics Committee of Pontifical Catholic University of Goiás. They were applied to 74 participants belonging to two groups: 40 patients with breast cancer and 34 controls (women who did not have cancer). Were included in this study women with 18 years or more seen at the Brazilian Center for Radiotherapy, Oncology and Mastology (CEBROM) in two situations:

- Those healthy, undergoing routine tests (control group);
- Those diagnosed with breast cancer (case group), who agreed to participate by signing the Informed Consent Form (ICF).

The questionnaires were applied in a highly complex oncology service in to treat breast cancer in Goiânia, Goiás, Brazil, from December 2015 to April 2016.

For comparative statistics, the  $\chi^2$  test for categorical variants and the t Student and ANOVA tests for continuous variants were used. The analyzes were made at BioEstat 5.0 software.

## RESULTS

The age variation of the control group was between 21 and 70 years, with a mean of 48.6 ( $\pm 12.2$ ) years. In the case group the mean age was 54.1 ( $\pm 13.2$ ) years, with a maximum of 79 and minimum of 33 years. Both groups presented homogeneity of ages ( $p=0.07$ ). In relation to weight, the variation was higher in the case group (minimum of 47 kg and maximum 110 kg), but the average was 66.3 ( $\pm 13.4$ ) kg, while the control group's average was 64.8 ( $\pm 8.6$ ) kg being the variation between 50 and 83 kg ( $p=0.561$ ). Regarding BMI (body mass index), the control group had an average of 25.31 ( $\pm 6.97$ ) kg/m<sup>2</sup> and average for the case group was 26.22 ( $\pm 6.09$ ) kg/m<sup>2</sup> ( $p=0.552$ ).

The age at menarche did not vary between the groups ( $p=0.242$ ), being, on average, 13 ( $\pm 2.0$ ) years for cases and 13.5 ( $\pm 1.7$ ) for controls. Also, the age of menopause did not change ( $p=0.654$ ) between groups, being 46.8 ( $\pm 4.2$ ) years in the control and 47.7 ( $\pm 6.8$ ) in cases.

Regarding the age of first pregnancy, patients with breast cancer had an average of 26.3 ( $\pm 7.3$ ) years, with a minimum of 15 and a maximum of 38 years. In the control group, the average was 24.5 ( $\pm 7.4$ ) years and ranged from 14 to 48 years ( $p=0.377$ ). About the number of children, cancer patients' average was of 1.7 ( $\pm 1.5$ ) children, and control patients' was of 1.6 ( $\pm 1.2$ ) ( $p=0.826$ ). This data can be seen in Table 1.

Regarding the use of contraceptives, 15 (37.5%) patients with breast cancer did not use them, and 25 (62.5%) used. At the control group, 5 (14.7%) did not use contraceptives and 29 (85.3%) used. In relation to hormone replacement therapy (HRT), 28 (70%) patients with breast cancer and 24 (70.6%) from the control group didn't use, while 12 (30%) patients with breast cancer and 10 (29.4%) from the control group made use of HRT.

About trouble at sleeping, 18 (45%) cases and 23 (67.6%) of controls didn't have, against 22 (55%) and 11 (32.4%), respectively, reported some difficulty. When asked about the room lighting while sleeping, 5% (2) of cancer patients were sleeping in a bright room (with light), 37.5% (15) in a room with dim light and 57.5% (23) were sleeping in a dark room. In controls, the percentages were, respectively, 5.9% (2) 41.2% (14) and 52.9% (18).

Regarding family history, the following variants were analyzed: cancer family history and breast cancer in the family. In cancer patients the percentages of these data were: 85% (34) had a history of cancer in the family, 70% (28) without breast cancer history in the family. In the controls, the results were, respectively, 73.5% (25) and 58.8% (20). As seen in Table 2.

Regarding chronotype, it was observed that, from 74 patients, 23.0% fit within the profile 'definitely matutinal' (DM); 45.9% were 'moderately matutinal' (MM); 21.6% 'Intermediate' (INT); 8.1% 'moderately vespertine' (MV); and 1.4% of 'definitely vespertine' (DV). When stratified between the groups, we observed that in cases with cancer, the rate was 15% DM, 47.5% MM, INT 30%, MV 5% and 2.5% DV; controls were 32.4% DM, 44.1% MM, 11.8% INT and also MV, but presented no profile definitely vespertine (Figure 1).

Assessing the shifts in which each patient had worked, it was observed that 44.4% of the patients with breast cancer and 47.1%

of the controls worked in the morning period. From those who worked in the evening shift, 42.9% were cases and 45.6% were controls; and 6.3% and 5.9%, respectively, worked on the night period. From those working full-time, 6.3% were cases and 1.5% controls. The average working time was 17 years in cases and 11.6 years in controls (Figure 2).

Data for chronotype and work shift can be seen in Table 3.

From the breast cancer patients analyzed, 70% (28) perform chemotherapy. From these, 50% (14) preferred to perform chemotherapy in the morning, 14.3% (4) preferred in the afternoon and 35.7% (10) said they were indifferent. Over the reported periods after chemotherapy, the worst collateral effects were 14.3% (4) in the morning and also in the evening; 10.7% (3) in the night; and 60.7% (17) reported being indifferent (Table 4).

## DISCUSSION

Risk factors for breast cancer may be related to both endocrine factors and reproductive history, as well as with behavioral and environmental factors. Among endocrine and reproductive history factors, one of the most important is prolonged exposure to estrogen, either endogenous or exogenously.<sup>11</sup> Obesity and desynchronization of the circadian cycle are part of behavioral and environmental factors.

From the results, some had no major changes when compared between two groups. The average age of menarche, for example, was 13 years in patients with breast cancer and 13.5 years in controls, with a minimum age of 10 and 11 years, respectively. In a study about the influence of hormonal factors in patients with breast cancer, data from 484 patients was analyzed. They found that the average age of menarche was 13.32 years and that the later was the age of menarche, the later was the age of diagnosis<sup>12</sup>. Although the average age of menarche between these patients is similar to the ones in the present study, it was not possible to correlate this data with the time of diagnosis, due to the lack of this type of data.

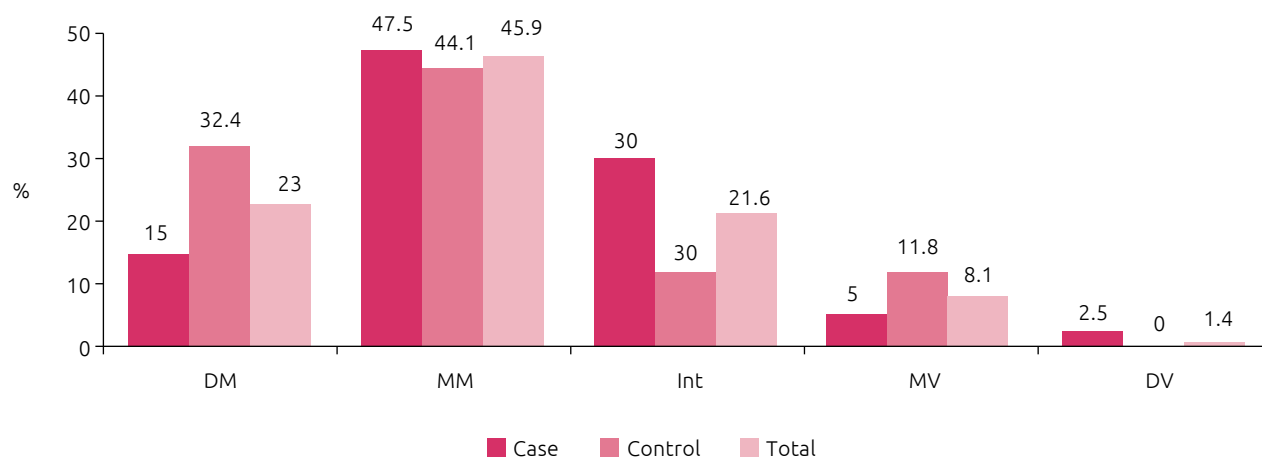
Likewise, the mean age of menopause was very similar, with 46.8 years in the controls and 47.7 in the cases and with maximum

**Table 1.** Characterization of the case and control groups to determine the medical, standard deviation (SD), extreme values and p-value.

Characteristic	Cases (n=40)				Controls (n=34)				p-value
	Average	SD	Minimum	Maximum	Average	SD	Minimum	Maximum	
Age (years)	54.1	13.2	33	79	48.6	12.2	21	70	0.070
Weight (Kg)	66.3	13.4	47	110	64.8	8.6	50	83	0.561
Height (m)	1.60	0.12	1.00	1.78	1.62	0.13	1.00	1.83	0.489
BMI (Kg/m <sup>2</sup> )	26.22	6.09	19.38	47.00	25.31	6.97	17.63	60.00	0.552
Menarche (years)	13.0	2.0	10	17	13.5	1.7	11	18	0.242
Menopause (years)	47.7	6.8	30	58	46.8	4.2	38	53	0.654
First Pregnancy (years)	26.3	7.3	15	38	24.5	7.4	14	48	0.377
Children (n)	1.7	1.5	0	7	1.6	1.2	0	4	0.826

**Table 2.** Frequency relative and absolute of the variants stratified by study group and control.

Characteristic	Cases (n=40)		Controls (n=34)		Total (n=74)		p-value
	n	F(%)	n	F(%)	n	F(%)	
Contraceptive							
No	15	37.5	5	14.7	20	27.0	0.0527
Yes	25	62.5	29	85.3	54	73.0	
Hormone Replacement Therapy							
No	28	70.0	24	70.6	52	70.3	0.8415
Yes	12	30.0	10	29.4	22	29.7	
Difficulty Sleeping							
No	18	45.0	23	67.6	41	55.4	0.0857
Yes	22	55.0	11	32.4	33	44.6	
Use 1 hour before bedtime							
Nothing	3	7.5	3	8.8	6	8.1	0.1651
Television	22	55.0	11	32.4	33	44.6	
Cell phone and Computer	9	22.5	8	23.5	17	23.0	
TV + cell phone and Computer	6	15.0	12	35.3	18	24.3	
Environment sleeps							
Bright (with light)	2	5.0	2	5.9	4	5.4	0.9288
Penumbra	15	37.5	14	41.2	29	39.2	
Dark	23	57.5	18	52.9	41	55.4	
Family History of Cancer							
No	6	15.0	9	26.5	15	20.3	0.3508
Yes	34	85.0	25	73.5	59	79.7	
Family Breast Cancer							
No	28	70.0	20	58.8	48	64.9	0.4476
Yes	12	30.0	14	41.2	26	35.1	
Physical Activity							
No	22	55.0	14	41.2	36	48.6	0.3409
Yes	18	45.0	20	58.8	38	51.4	
Alcoholic Beverage							
No	35	87.5	28	82.4	63	85.1	0.7700
Yes	5	12.5	6	17.6	11	14.9	



DM: definitely matutine; MM: moderately matutine; Int: intermediate; MV: moderately vespertine; DV: definitely vespertine.

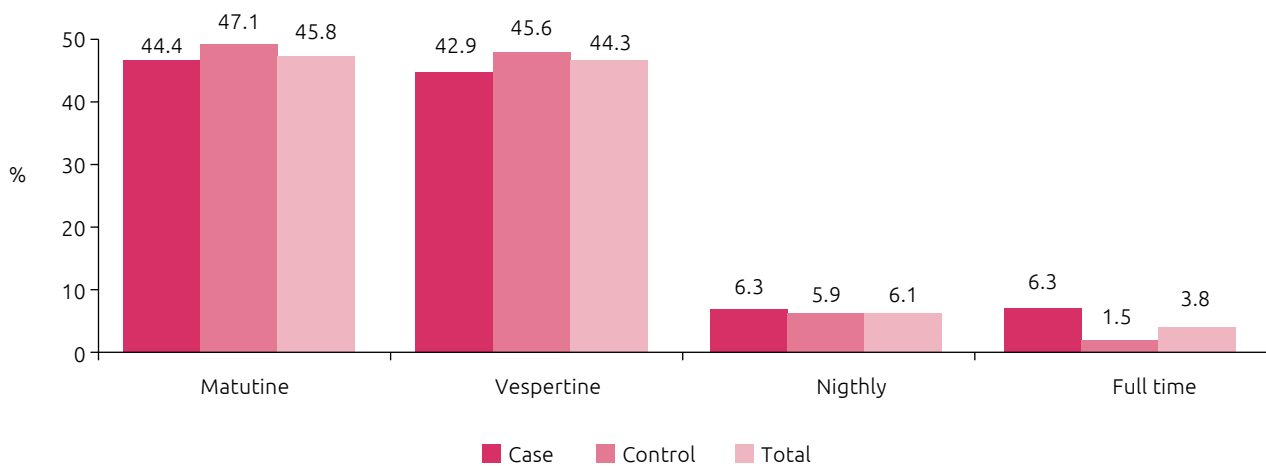
**Figure 1.** Chronotype profiles for the case, control and total groups.

age of 53 and 58, respectively. On the average of both variants (menarche and menopause), it is observed that the time of exposure to estrogen did not vary between the groups. That is, both cases of breast cancer as controls, were exposed to estrogen for a similar period of time.<sup>12</sup>

Concerning the age of first pregnancy, the groups had an average of 26.3 years in cancer patients and 24.5 years in controls, being the maximum 48 and 38 years, respectively. This data is relevant, since it is known that the development of first pregnancy is important for the maturation of breast cells to confer more protection from the action of carcinogens.<sup>13</sup> Due to the similarity of the average age, it was also not possible to consider this data as a risk factor. In a study with women in two cities in

northeastern Brazil, it was observed that the age at last pregnancy represented a more significant risk for the disease than the age at first pregnancy.<sup>13</sup>

Regarding the use of contraceptives, in patients with breast cancer, 15 (37.5%) women said they never used, while in the control group 5 (14.7%) women said that. Among those who have confirmed the use of contraceptive, during all life period, accounted for 25 (62.5%) women in the case group and 29 (85.3%) in the control group ( $p=0.0527$ ). Still in this study with 484 women, the authors showed that the age of diagnosis was significantly higher in patients who did not use contraceptive compared to those who did, despite the time of use, there wasn't a significant relationship with the age of breast cancer's diagnosis.<sup>13</sup>



**Figure 2.** Work shifts for the case, control and total groups were divided into matutine, vespertine, nightly and full-time.

**Table 3.** Relative and absolute frequency of chronotypes and turns with their p-values.

Characteristic	Cases (n=40)		Controls (n=34)		Total (n=74)		p-value
	n	f(%)	n	f(%)	n	f(%)	
Chronotype							
Definitely Matutinal	6	15.0	11	32.4	17	23.0	0.1563
Moderately Matutinal	19	47.5	15	44.1	34	45.9	
Indifferent	12	30.0	4	11.8	16	21.6	
Moderately Vespertine	2	5.0	4	11.8	6	8.1	
Definitely Vespertine	1	2.5	0	0.0	1	1.4	
Shift							
Morning	28	44.4	32	47.1	60	45.8	0.5412
Afternoon	27	42.9	31	45.6	58	44.3	
Night	4	6.3	4	5.9	8	6.1	
Full time	4	6.3	1	1.5	5	3.8	
Total	63		68		131		
Chronotype × Shift							
Harmonic	11	17.5	5	7.4	16	12.2	0.0827
Disharmonic	19	30.2	29	42.6	48	36.6	

On the use of hormone replacement therapy (HRT), 30% (20) of patients with breast cancer made use of this therapy, while 70% (28) did not; at the controls, 70.6% (24) did not use and 29.4% (10) did. According to the Collaborative Group on Hormonal Factors in Breast Cancer, the use of hormone replacement therapy was related to increased breast cancer, and the risk also increased with continuous hormone therapy. In a second study, both the use of estrogen alone and combined with progesterone also showed an increased risk of developing breast cancer.<sup>13</sup> But in another study, 78.9% of patients with breast cancer, studied for this variant, did not use HRT, which is similar to the findings of this research.<sup>13</sup>

The desynchronization of circadian cycle is seen in some longitudinal studies as a major risk factor for developing breast cancer. Besides Nurses' Health Study, another study with flight attendants working at discordant times of their circadian rhythm, found that this enables the development of breast cancer.<sup>10</sup> Another several international studies in blind women showed a lower incidence of cancers, including breast cancer. It's justified because they have little or none exposure to light at night and thereby they wouldn't have reduced levels of melatonin.<sup>7</sup>

One of the theories that justify this association is the suppression of melatonin production. This hormone, produced by the pineal gland and suppressed by light, plays a central role in the synchronization process of circadian rhythms.<sup>14</sup> In addition

to its action and influence of the secretion of hormones (such as estrogen)<sup>8</sup> there is also the oncostatic action to alter the cell cycle by inhibiting mitosis, partially delaying metaphase, and also strengthening the immune system, removing free radicals and stimulated expression of the tumor suppressor gene, such as p53.<sup>8</sup>

From the collected data, it was possible to assess that among all cases, 6.3% worked both night shifts or full-time, whereas in the control this value was 5.9 and 1.5%. From the patients with breast cancer, 44.4% worked in the morning and 42.9% in the evening. Furthermore, when asked about the environment in which they slept, 5% of the cancer patients slept in a lighting room; 37.5% slept in penumbra and 57.5% in the dark. At the controls, 5.9% sleep with light; 41.2% in penumbra and 52.9% in the dark. These data are relevant because both work in the night and sleep in bright environments, where there is the inhibitory action of light on the release of melatonin.

Another important factor is the suppression of sleep, causing changes in the regulation and in biological clock genes' activity. In a study that evaluated 17 men in two sessions (in one of them, patients slept the night and in the other they stayed awake), the authors were able to demonstrate, through samples collected at these two moments, that epigenetic mechanisms caused chemical changes in the DNA molecule, which regulates how genes are activated or inactivated.<sup>15</sup> These changes, observed in night shift workers and even in patients with type 2 diabetes, could lead to changes in the genome of the tissues and affect the metabolism for longer periods.

From the patients analyzed, 55% patients with breast cancer and 32.4% of controls had some type of difficulty in sleeping. Based on the study above, it may be necessary to collect samples to highlight the possible chemical changes in these patients' DNA molecule.

Another data analyzed was the relationship between chronotype and shift work in patients with breast cancer and controls. The fact that someone prefers to perform their activities in a given period, as the morning, for example, is nothing more than an endogenous interindividual component that is essential for the biological clock. Relying on diurnal preference, it is possible to set different types of chronotypes, ranging from matutinal, vespertine, until intermediary.<sup>3</sup> By  $\chi^2$ , the characteristics between case and control groups were similar, so it wasn't possible to confirm the relationship between working out of chronotype's best time and breast cancer.

In this study, 28 (70.0%) patients did chemotherapy. Referring which period they felt better doing chemotherapy, 50.0% showed preference to the morning shift, while 35.7% said they were indifferent. When the preferred period for the completion of chemotherapy was contrasted with chronotype, it was noticed that most of the patients (53.6%) were within the chronotype "moderate matutinal" and, from these, 46.7% used chemotherapy in the morning.

**Table 4.** Cases of patients undergoing chemotherapy.

Characteristic	Cases (n=28)	
	n	f(%)
Chemotherapy		
No	8	20.0
Yes	28	70.0
Not Available	4	10.0
Best period for chemotherapy		
Morning	14	50.0
Evening	4	14.3
Indifferent	10	35.7
Best Chemotherapy × Chronotype		
Definitely Matutinal	4	14.3
Moderately Matutinal	15	53.6
Indifferent	7	25.0
Moderately Vespertine	1	3.6
Definitely Vespertine	1	3.6
Worst Period Collateral Effects		
Morning	4	14.3
Evening	4	14.3
Night	3	10.7
Indifferent	17	60.7

Regarding the time that most felt the impact of collateral effects of chemotherapy, the majority (60.7%) declared indifferent. When the most critical period for the collateral effects of chemotherapy was contrasted with chronotype, it was noticed that 80.0% of patients had desynchronization. This desynchronization is due to perform chemotherapy in times of the day that doesn't match their chronotypes. It is known that the occurrence of adverse effects due to patient's intolerance to medication, considering the time of the day that they are administered.<sup>16</sup>

Understanding this, it is possible to administer the cytostatic maximizing its actions, simultaneously increasing the effectiveness of the treatment and reducing collateral effects.<sup>2</sup>

## CONCLUSION

This study could not correlate the oncogenesis of breast cancers and labor activity occurring in a different shift of the individual's chronotype. This subject still needs further studies.

## REFERENCES

1. Rana S, Mahmood S. Circadian rhythm and its role in malignancy. *J Circadian Rhythms*. 2010;8:3-13. <https://dx.doi.org/10.1186%2F1740-3391-8-3>
2. Marcos AFS. O ciclo circadiano na suscetibilidade para patologias oncológicas e na sua terapêutica [dissertação]. Algarve: Universidade do Algarve; 2012.
3. Alam MF. A relevância da Cronobiologia no processo saúde-doença: relação do Cronotipo com o estilo de vida e saúde [tese]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2012.
4. Bueno C, Wey D. Gênese e ontogênese do ritmo sono/vigília em humanos. *Rev Biologia*. 2012;9(3):62-7. <https://dx.doi.org/10.7594/revbio.09.03.12>
5. Baessa DJ. Níveis de atenção e capacidade de concentração de nadadores adultos com diferentes cronotipos [dissertação]. Curitiba: Universidade Federal do Paraná; 2011.
6. Pereira EF, Anacleto TS, Louzada FM. Interação entre sincronizadores fóticos e sociais: repercussões para a saúde humana. *Rev Biologia*. 2012;9(3):68-73. <https://dx.doi.org/10.7594/revbio.09.03.13>
7. Izu M, Cortez EA, Valente GC, Silvino ZR. Trabalho noturno como fator de risco na carcinogênese. *Ciênc Enferm*. 2011;17(3):83-95.
8. Sasso EM. Avaliação do efeito da dessincronização circadiana sobre o câncer de mama e utilização terapêutica de melatonina em ratas sprague-dawley [dissertação]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2013.
9. Gemelli KK, Hilleshein EF, Lautert L. Efeitos do trabalho em turnos na saúde do trabalhador: revisão sistemática. *Rev Gaúcha Enf*. 2008;29(4):639-46.
10. Stevens RG. Light-at-night, circadian disruption and breast cancer: assessment of existing evidence. *Int J Epidemiol*. 2009;38(4):963-70. <https://doi.org/10.1093/ije/dyp178>
11. Instituto Nacional de Câncer. Coordenação de Prevenção e Vigilância. Estimativa 2014: Incidência de Câncer no Brasil. Rio de Janeiro: Ministério da Saúde; 2014.
12. Eidt ER, Ramos RL, Scopel DD, Cararo PG, Victorino MF. Avaliação dos fatores hormonais em mulheres com diagnóstico de neoplasia de mama com idade superior a 40 anos. *Arq Catarin Med*. 2011;40(1).
13. Santos AB, Araújo MC. Fatores de risco em mulheres com câncer de mama atendidas no centro de diagnóstico Nossa Senhora do Rosário em Santa Maria-RS. *Disciplinarum Scientia*. 2012;13(1):63-70.
14. Levandovski RM. Perfil Cronobiológico em Amostra Populacional Caucasiana: Abordagem Cronobiológica dos Sintomas Depressivos [tese]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2011.
15. Cedernaes J, Osler ME, Voisin S, Broman JE, Vogel H, Dickson SL, et al. Acute Sleep Loss Induces Tissue-Specific Epigenetic and Transcriptional Alterations to Circadian Clock Genes in Men. *J Clin Endocrinol Metab*. 2015;100(9):E1255-61. <https://doi.org/10.1210/JC.2015-2284>
16. Silva RBG. Cronoterapia- Uma abordagem temporal da terapêutica [dissertação]. Portugal: Universidade Fernando Pessoa; 2011.

# BREAST ULTRASOUND IN THE INTERIOR OF THE STATE OF SANTA CATARINA, BRAZIL

## Ultrassom de mama no interior do estado de Santa Catarina

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### ABSTRACT

Breast ultrasound is an essential tool in Mastology. This technology can help in the diagnosis of lesions affecting the mammary gland, identifying both benign and malignant tumors. However, ultrasound examination has precise indications in medical practice; and should be indicated cautiously, as one should not think it can tackle all diagnoses of the breast. In this paper, the author assesses 197 breast ultrasounds in the city of Chapecó, Santa Catarina, Brazil. The author reports lack of clinical criteria in many indications of ultrasound examination by health professionals at Basic Health Units of the city.

**KEYWORDS:** Breast; screening; ultrasonography, mammary.

### RESUMO

O exame de ultrassom de mama é imprescindível em mastologia. Essa tecnologia pode ajudar no diagnóstico de lesões que acometem a glândula mamária, identificando tumores tanto benignos como, possivelmente, malignos. Entretanto, o uso desse exame tem indicações precisas na prática médica. Ele deve ser pedido com critério e não se deve acreditar que solucionará todos os diagnósticos das lesões mamárias. Neste trabalho, o autor analisa 197 pedidos de exame de ultrassom de mama, realizados na cidade de Chapecó (SC). O autor atribui a falta de critério clínico em muitas indicações para o exame de ultrassom pelos profissionais de saúde que atendem nas Unidades Básicas de Saúde da cidade.

**PALAVRAS-CHAVE:** Mamas; rastreamento; ultrassonografia mamária.

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## INTRODUCTION

The importance of breast ultrasound in the diagnosis of breast tumors of various types is unquestionable. This examination is becoming more common in mastology, complementing clinic and mammographic assessments. Initially, its use was limited to the differentiation of solid tumors and mammary cysts. The present equipment allows to evaluate anatomical changes of the breasts in details, thus being fundamental in mastology practice. Modern ultrasound devices are highly sensitive and specific<sup>1</sup> and, according to Stavros<sup>2</sup>, are aimed to identify palpable breast abnormalities or alterations spotted by mammographic examination.

In some cases, breast ultrasound is used as a means of screening patients at increased risk for breast cancer. This practice is not supported by the Brazilian College of Radiology and Diagnostic Imaging or by the Brazilian Society of Mastology and the Brazilian Federation of Gynecology and Obstetrics Associations<sup>3</sup>.

The author of the present study evaluated 197 requests of this exam for users of the municipal public health service in the city of Chapecó, western Santa Catarina. When analyzing the profile of patients referred to the exam and the data extracted from the medical orders, many of them were found to be not justifiable. A survey on these data may contribute to better strategies in women's health programs across the municipality.

## MATERIAL AND METHODS

The city of Chapecó, located in the west of Santa Catarina, has approximately 200 thousand inhabitants and is the most important in the region. The Health Secretariat tries to provide the population with assistance in several centers and to deliver good health to those serviced by different Basic Health Units (UBS).

Women assisted at the UBSs with breast-related complaints are evaluated at the units and sent to appointments with gynecologists or mastologists. Not all UBS have professionals with specific qualifications to care for gynecology and/or mastology, but all of them have physicians practicing general medicine or working for the Family Health Program. Breast imaging is mostly performed at a clinic dedicated to women, which is run by the Health Secretariat and located in a central area of the city. Few exams are performed by private clinics that have an alliance with the public system.

The information found in ultrasound orders was divided into three groups: patients' personal information, referral for examination, and specialty of the professional ordering it. As these were already included in medical orders that had been sent to the Women's Clinic, signature of the informed consent form was not required.

The author created a method of identification of patients in each questionnaire, noting their initials at the top right of the medical record along with the date of exam performance.

Keeping these documents and confidentiality of data collected by the research instrument was his responsibility.

The information collected was analyzed based on the percentage obtained, and the statistical test  $\chi^2$  was applied when necessary.

A copy of the project was sent to the Ethics Committee of the Health Secretariat, which approved the research in full, so that the study could be conducted.

## RESULTS

The questionnaire was divided in three parts. The first part contains the profile of women referred for ultrasound (Table 1).

The second session of the questionnaire analyzes the medical requests for ultrasound examination of 197 women included in the study (Table 2). "Breast nodule", as expected, was the most cited reason for imaging examination.

**Table 1.** Percentage of women referred for breast ultrasound.

Age	N	%
15-25 years	27	14
>25-35 years	72	36
>35 years	98	49
Marital Status		
Single	41	21
Married	105	53
Widow	15	7
Stable union	20	10
Split	16	8
Parity		
Zero	43	22
1-4 children	145	73
>4 children	9	4
Health coverage		
SUS	183	93
Other insurances	14	7
Non household-related work		
Yes	93	47
No	104	53
Previous ultrasound		
Yes	82	41
No	115	58
Breast cancer Family history*		
Yes	49	25
No	146	74

SUS: Brazilian Public Health System; \*two patients could not inform about family history.

Table 3 shows the field of acting of physicians who requested breast ultrasound examination. Most physicians working at the UBS act as general physicians and in the Family Health Program, which explains the high percentage of requests by these professionals.

Family history of breast cancer might motivate the increase in requests for breast ultrasound by professionals specialized in women's health, when compared to general practitioners and/or PSF professionals. However, family history was not statistically significant when requests for breast ultrasound by general practitioners and by women's health specialists were compared (Table 4).

## DISCUSSION

A total of 197 women were referred to the Women's Clinic for breast ultrasound examination for various reasons in the course of five months. A questionnaire designed by the author was applied to this group to evaluate the profile of patients referred. Clinical indications, previous examination — of any — and breast cancer family history were analyzed as possible influence on examination request.

**Table 2.** medical reason for breast ultrasound examination.

Indication	N	%
Breast nodule	77	39
Complementary to mammography	57	29
Breast tenderness	31	15
Routine	16	8
Post-surgical control after papillary discharge	8	4
Not informed	8	4

**Table 3.** Specialties of physicians who requested breast ultrasound.

Professional	N	%
General practitioner and Family Health Program	117	59
Women's health	72	37
Other specialties	8	3

**Table 4.** Breast Family history\* as the reason for breast ultrasound request

	Positive	Negative
Specialist in women's health	24	47
General practitioner and Family Health Program	28	96

p=1.54; \*two patients did not know if there were breast cancer history in their families.

Patients eligible for the examination were supposed to be <35 years old, according to Dixon<sup>1</sup>. Henderson considers an even lower age (30) when a nodule is discovered and the mammogram does not help due to higher density of breast tissue<sup>4</sup>. This study showed that nearly half (49%) of these women were out of the age group proposed by authors such as Dixon<sup>1</sup>. The other half of patients referred for breast ultrasound would probably have been better evaluated by clinical examination and mammography.

In this study, complementary imaging, mammography, and ultrasound were performed in 29% of patients referred. Professor Thomas Stavros states in one of his many papers that only three breast cancers are diagnosed every 1,000 screening mammograms, which is equivalent to 0.3%<sup>2</sup>. Applying this percentage to this 197 population, conclusion is that breast cancer diagnosis would not reach 1%. The lack of knowledge about the study by Stavros, added to the uncertainty of mammography assessment and suggestion of complementary ultrasound by radiologists at the time of report writing can explain why almost 1/3 of women were referred for breast ultrasound.

Breast cancer family history did not result in greater number of ultrasound requests by gynecologists and/or mastologists of the Health Secretariat as compared to requests by general practitioners or physicians of the family health strategy. The percentage of requests for patients with family history by specialists was 12%, while among physicians referred to as generalists or taking part in the family health program the score was 14%.

The clinical complaint of breast nodules was the main reason for breast ultrasound indication among 197 patients. Specific works on this matter also point to breast nodules as the main reason for such request<sup>5</sup>. Zabolotskaya<sup>6</sup> reported that malignant breast tumors appear in the upper outer quadrant of the breast in more than 50% of cases; in the upper inner quadrant in 15% of cases; in the lower outer quadrant in 10% of cases, in the upper inner quadrant in 5% of cases.

The research conducted in the municipality of Chapecó, Santa Catarina, also showed that breast pain complaint was the second most common reason for breast ultrasound (15%). According to Dixon, this reason is not routine for this type of examination<sup>1</sup>.

Breast ultrasound is not an instrument for breast cancer screening. It is of great value for clinical situations such as breast tenderness according to the consensus report from a meeting on this subject matter<sup>3</sup>. Mammography is the only breast cancer screening test that can reduce mortality from this disease, according to Tabar<sup>7</sup>, although the study ACRIN 6666 has shown that breast ultrasound as complement to mammography increases the rate of detection of compared to mammography only<sup>8</sup>.

It is undeniable that breast ultrasound is of great utility for medical practice, usually conducted in a targeted manner, following mammography and clinical examination, to provide a more specific diagnosis of compared to each method alone<sup>2</sup>. From 1980, breast ultrasound was added to the set of imaging exams commonly requested, especially in mastology<sup>5</sup>. However, when analyzing data

obtained from this first research, the author believes that deeper knowledge about breast ultrasound indication is required so that women can really benefit from being evaluated at the UBS of the city of Chapecó. The author also believes that such study is based on conclusions previously reported by Porter and Teinsberg, who emphasized the correct use of technological resources for health care efficacy and no waste of resources in medical practice<sup>9</sup>.

## CONCLUSION

The study carried out in the city of Chapecó, Santa Catarina, to assess 197 requests for breast ultrasound examination, brings about the need to better qualify health professionals hired in UBS so they can perform this examination and identify which patients would actually benefit from it, thus reaching the best practical result and minimizing the waste of resources.

## REFERENCES

1. Dixon A-M. Breast Ultrasound How, Why and When. Londres: Churchill Livingstone/Elsevier; 2008.
2. Stavros AT. Tratado de Ultrassonografia Diagnóstica. 4ª ed. Missouri: Mosby/Elsevier; 2012. v.2.
3. Urban LABD, Chala LF, Bauab SP, Schaefer MB, Santos RP, Maranhão NMA, Kefalas AL, Kalaf JM, Ferreira CAP, Canella EO, Peixoto JE, Amorim HLE, Camargo Junior HSA. Breast Cancer Screening: Updated Recommendations of the Brazilian College of Radiology and Diagnostic imaging, Brazilian Breast Society, and Brazilian Federation of Gynecological and Obstetrical Associations. *Mastology*. 2017;27(3):258-64. <http://doi.org/10.5327/Z2594539420170000246>
4. Henderson C. Breast Cancer: Fundamental of Evidence-Based Disease Management. Oxford: Oxford University Press; 2015.
5. Sencha A. Breast Ultrasound. Nova York: Springer; 2013.
6. Zabolotskaya NV. Ultrasound diagnosis of Breast. In: Mitkov VV (Ed.). Practical guidance on ultrasound diagnosis. Vidar, Moscow: Ed Vidar; 2006. p.563-607.
7. Tabar L, Vitak B, Chen TH, Yen AM, Cohen A, Tot T, et al. Swedish two-country trial: impact of mammographic screening on breast cancer mortality during 3 decades. *Radiology*. 2011;260:658-63. <https://doi.org/10.1148/radiol.11110469>
8. Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Böhm-Vélez M, et al. Combined screening with ultrasound and mammography alone in women at elevated risk of breast cancer. *JAMA*. 2008;299:2151-63. <https://doi.org/10.1001/jama.299.18.2151>
9. Porter EM, Teisberg OE. Repensando a Saúde. Estratégia para melhorar a qualidade e reduzir os custos. São Paulo: Bookman; 2007.

# AXILLARY SURGERY IN BREAST CANCER: ACUTE POSTOPERATIVE COMPLICATIONS IN A HOSPITAL COHORT OF WOMEN OF RIO DE JANEIRO, BRAZIL

Abordagem cirúrgica axilar no câncer de mama: complicações pós-operatórias agudas em uma coorte hospitalar de mulheres do Rio de Janeiro

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## ABSTRACT

**Objective:** To analyze the incidence of early postoperative complications in women with breast cancer according to the axillary surgery. **Methods:** An observational study of a cohort of women diagnosed with T1-T2N0M0 clinical stage breast cancer attended at the Brazilian National Cancer Institute from January 2007 to December 2009. The outcome was defined as post-surgical complications in the affected upper limb, such as: axillary web syndrome, winged scapula, paraesthesia and surgical wound, seroma and wound infection. The incidence of simple complications was estimated. The crude and adjusted Odds Ratios, with their respective 95% confidence intervals, were estimated by Multiple Logistic Regression analysis. **Results:** The incidence of postoperative complications was significantly lower in sentinel lymph node biopsy (axillary web syndrome: 6.0%; paraesthesia: 45.2%; winged scapula: 9.1%; seroma: 28.5%; wound infection: 3.8%) than in axillary lymphadenectomy (axillary web syndrome: 22.5%; paraesthesia: 89.8%; winged scapula: 50.0%; seroma: 69.4%; wound infection: 12.9%). Compared to those who underwent axillary lymphadenectomy, the risk of postoperative complications in those in whom sentinel lymph node biopsy was performed was significantly lower. **Conclusion:** The sentinel lymph node biopsy technique was an independent protective factor for acute postoperative complications when compared to axillary lymphadenectomy.

**KEYWORDS:** Breast neoplasms; lymphadenectomy; postoperative complications; sentinel lymph node biopsy.

## RESUMO

**Objetivo:** Analisar a incidência de complicações pós-operatórias precoces em mulheres com câncer de mama de acordo com a cirurgia axilar. **Métodos:** Estudo observacional de uma coorte de mulheres diagnosticadas com câncer de mama em estágio clínico T1-T2N0M0 atendidas no Instituto Nacional de Câncer do Brasil de janeiro de 2007 a dezembro de 2009. O desfecho foi definido como complicações pós-cirúrgicas no membro superior afetado, tais como: síndrome da rede axilar, escápula alada, parestesia e ferida cirúrgica, seroma e infecção da ferida. A incidência de complicações simples foi estimada. Os Odds Ratios bruto e ajustado, com seus respectivos intervalos de confiança de 95%, foram estimados por análise de Regressão Logística Múltipla. **Resultados:** A incidência de complicações pós-operatórias foi significativamente menor na biópsia de linfonodo sentinela (síndrome da rede axilar: 6,0%; parestesia: 45,2%; escápula alada: 9,1%; seroma: 28,5%; infecção da ferida: 3,8%) do que na linfadenectomia axilar (síndrome da rede axilar: 22,5%; parestesia: 89,8%; escápula alada: 50,0%; seroma: 69,4%; infecção da ferida: 12,9%). Em comparação com aqueles que foram submetidos a linfadenectomia axilar, o risco de complicações pós-operatórias naqueles nos quais a biópsia de linfonodo sentinela foi realizada foi significativamente menor. **Conclusão:** A técnica de biópsia de linfonodo sentinela foi um fator de proteção independente para complicações pós-operatórias quando comparadas à linfadenectomia axilar.

**PALAVRAS-CHAVE:** Neoplasias da mama; excisão de linfonodo; complicações pós-operatórias; biópsia de linfonodo sentinela.

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## INTRODUCTION

Breast cancer is the most frequent tumor site and the leading cause of cancer death among women worldwide, with an incidence ranging from 31.3 per 100.000 women in developing countries, such as Brazil, to 73.4 per 100.000 women in developed countries in 2012<sup>1</sup>. There is evidence that the actions for the early detection of breast cancer are still ineffective in Brazil, leading to diagnoses in advanced stages. A study carried out in the country<sup>2</sup> used the Database of Hospital Cancer Registries in Brazil between 2000 and 2009, and included 59.317 women with breast cancer. This study showed that only 19.1% of women were diagnosed in stage I and 53.4% in advanced stages, in which aggressive treatments are necessary and several adverse effects can result from them, such as early and late postoperative complications in the upper limb homolateral to the surgery<sup>2</sup>.

Among the early postoperative complications, the axillary web syndrome, paraesthesia, winged scapula, seroma and surgical wound infection are recognized<sup>3</sup>. In women with early-stage breast cancer, the surgical approach may be more conservative, depending on the presence or absence of axillary involvement. Thus, for adequate axillary staging, the surgical treatment of breast cancer involves an approach through axillary lymphadenectomy (AL) and/or sentinel lymph node biopsy (SLNB). AL is associated with an increase in early postoperative morbidities, and to minimize such complications, SLNB was incorporated, marking the advancement of breast surgical treatment. It is considered the preferred method of staging breast cancer in patients with clinically negative axilla with T1 or T2 classification<sup>4,5</sup>. Although some studies report the presence of early morbidities in women submitted to SLNB, the frequency is lower than in AL<sup>6-8</sup>.

In Brazil, few studies have addressed the comparison of early complications according to the axillary approach, focusing mostly on AL<sup>9-11</sup>, while those describing the incidence in both axillary approach evaluated only a few complications<sup>12-16</sup>. Therefore, the aim of the present study is to estimate the risk of early postoperative complications according to the axillary surgical approach.

## METHODS

An observational study was performed in a cohort of women with breast cancer and clinical stage T1 and T2N0M0 enrolled and attended at the Hospital of Cancer III (HCIII/INCA), from Jan/2007 to Dec/2009. The patients were identified by the Hospital Cancer Registry of HCIII/INCA (HCR/HCIII), using electronic and physical records. Data collection was performed based on the physiotherapy and nursing service reports, using a standardized form. This study was approved by the Ethics and Research Committees of the National Cancer Institute (INCA) and Sérgio Arouca National School of Public Health (ENSP).

Among the 1.417 women (clinical stage T1-T2N0M0) identified at the database, 210 (14.8%) presented different clinical

stages from T1-T2N0M0 on medical reports; 108 (7.6%) had in situ histological type; 28 (2.0%) did not undergo surgery or did not undergo an axillary approach; 11 (0.8%) had previous cancer; 40 (2.8%) had previous contralateral and/or homolateral breast cancer; 42 (3.0%) had bilateral synchronous breast cancer; and 18 (1.3%) had undergone treatment (completely or partially) outside the INCA. Twenty-seven patients (1.9%) were lost due to the non-identification of physical records. Thus, 933 women with tumors with up to 5 cm, clinically negative axilla and absence of distant metastasis, were included in the present study.

Sociodemographic, clinical and lifestyle information were collected. The exposure was the axillary surgical approach, defined as SLNB or AL, and then categorized into: SLNB only, SLNB followed by AL or AL only. The outcome was defined as postoperative complications in the affected upper limb and surgical wound. Information on upper limb complications (axillary web syndrome, winged scapula, paraesthesia and surgical wound, seroma and wound infection) were collected in the 1st evaluation of the physiotherapy sector that may have occurred within 3 months after the surgery. Information about the complications that occurred in the operative wound (seroma and wound infection) were collected from the nursing reports.

Axillary web syndrome (AWS) was defined as the presence of palpable and/or visible fibrous cords in the axilla or along the upper limb homolateral to the surgery, being more frequently observed with elevation and abduction of the upper limb. The winged scapula (WS) was considered the condition in which the medial border and lower angle of the scapula become more prominent in the thorax. It was assessed by visual observation during active elevation of the upper limbs or by the Hoppenfeld test, which consists of the patient standing in orthostatic posture, flexing shoulders at 90 degrees, joining hands, laying flat on the wall and extending the elbows, and pushing hands against the wall. The paraesthesia of the region innervated by the intercostobrachial nerve was defined by the presence of burning pain, shooting pain, pressure sensation and numbness in the lateral region of the thorax, medial region of arm and/or axilla, being assessed by touch and/or referenced by the patient. Seroma was defined by the nursing report as a collection of fluids formed after removal of the suction drain and located in the breast, and/or axilla requiring aspiration. The surgical wound infection (WI) was identified through nursing reports of infection associated with the use of antibiotic therapy.

Mean, median and standard deviation of continuous variables was estimated, while categorical variables were evaluated by frequencies. Differences between the means were evaluated using the Mann-Whitney test for continuous variables. Differences between proportions were assessed using the chi-square test. A significant level of 5% was considered for both tests.

The incidence for each acute complication was estimated, and the crude and adjusted odds ratios (OR) and their respective

95% confidence intervals were performed using the Logistic Regression analysis. A multivariate analysis was carried out to estimate the effect of the axillary approach on each acute complication, adjusted by confounding variables. The inclusion criteria in the multivariate analysis was the biological relevance or a  $p < 0.20$  in the crude analysis. The exclusion criteria of the model was a  $p > 0.05$  in the model. Statistical significance was calculated using the Wald statistic. The model adjustment was verified by residue analysis. All analyses were performed using the Statistical Package for Social Science (20.0 version).

## RESULTS

The mean age of the study population was 57.9 years ( $\pm 12.6$ ), with an average of 2 lymph nodes removed ( $\pm 1.19$ ) in patients submitted to SLNB alone, 17.8 ( $\pm 5.35$ ) in those submitted to

SLNB  $\pm$  AL, and 18.1 ( $\pm 6.30$ ) in those who underwent AL directly. Regarding nutritional status, the mean Body Mass Index (BMI) was  $29.2 \text{ kg/m}^2$  ( $\pm 32.2$ ), with 68.8% of the women being classified as overweight or obese. Around 53% reported being housewives, 11.7% of the women were smokers and 24.7% had a habit of consuming alcoholic drinks. In the comparison between groups, it was observed that those submitted to AL at the diagnosis of breast cancer were significantly older ( $>60$  years: 67.9%) when compared to women who had SLNB (43.8%) and SLNB followed by AL (33.3%), and had house activities as their main occupation (AL: 72.1%, SLNB $\pm$ AL: 47.9%, SLNB: 51.4%) (Table 1).

Clinical and treatment variables distribution according to the axillary approach (Table 1) revealed that the majority of women had clinical stage I (61.6%), underwent conservative surgery (52.8%), and were not submitted to breast reconstruction (83.7%). Regarding the axillary approach, 73.2% of the women

**Table 1.** Distribution of socio-demographic characteristics, nutritional status, clinical status and treatment according to the axillary approach of the cohort of women with breast cancer (T1-2N0M0).

Variables	N total (%) or mean (SD)	Axillary Surgery (%)			$\chi^2$ p-value
		SLNB	SLNB+AL	AL	
Age (mean $\pm$ SD)	57.9 (12.6)	57.3 (DP=12.2)	55.0 (DP=12.2)	59.9 (DP=13.9)	
Age					
<40	55 (5.9)	41 (6.0)	13 (9.0)	1 (0.9)	<0.001
40–59	459 (49.2)	343 (50.2)	83 (57.6)	33 (31.1)	
$\geq 60$	419 (44.9)	299 (43.8)	48 (33.3)	72 (67.9)	
Occupation					
Unemployed	35 (3.8)	28 (4.1)	4 (2.8)	3 (2.9)	0.001
External job	398 (43.0)	301 (44.5)	71 (49.3)	26 (25.0)	
At home	492 (53.2)	348 (51.4)	69 (47.9)	75 (72.1)	
BMI					
Underweight	36 (3.9)	30 (4.4)	5 (3.5)	1 (1.0)	0.471
Suitable	254 (27.3)	193 (28.3)	34 (23.6)	27 (25.7)	
Overweight	334 (35.8)	244 (35.7)	53 (36.8)	37 (35.2)	
Obesity	308 (33.0)	216 (31.6)	52 (36.1)	40 (38.1)	
Clinical Stage					
T1N0M0 (I)	575 (61.6)	478 (70.0)	65 (45.1)	32 (30.2)	<0.001
T2N0M0 (IIA)	358 (38.4)	205 (30.0)	79 (54.9)	74 (69.8)	
Type of Breast Surgery					
Conservative	493 (52.8)	423 (61.9)	61 (42.4)	9 (8.5)	<0.001
Mastectomy	440 (47.2)	260 (38.1)	83 (57.6)	97 (91.5)	
Breast Reconstruction					
No	781 (83.7)	557 (81.6)	124 (86.1)	100 (94.3)	<0.001
Immediate	124 (13.3)	109 (16.0)	14 (9.7)	1 (0.9)	
Late	28 (3.0)	17 (2.5)	6 (4.2)	5 (4.7)	

\*The difference in sample size corresponds to the absence of information; SD: standard deviation; SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; BMI: body mass index.

underwent SLNB, 15.4% SLNB followed by AL, and 11.4% underwent firstly AL. Most women (66.4%) removed 1 to 3 lymph nodes, and 24.7% removed more than 10. Compared to women with SLNB, women submitted to AL presented statistically more advanced clinical stage (SLNB: 30%; SLNB+AL: 54.9%; AL: 69.8%), a greater frequency of mastectomy (SLNB: 38.1; SLNB+AL: 57.6%; AL: 91.5%) and removed more than 10 lymph nodes (SLNB: 0%; SLNB+AL: 94.4%; AL: 89.5%).

The incidence of surgical WI (3.8%) and seroma (28.5%) was statistically lower in women submitted to SLNB than in those submitted to AL (69.4% for seroma, and 12.9% for infection) ( $p=0.000$ ). Compared to women submitted to AL, those who underwent SLNB presented a statistically lower incidence of the AWS (AL: 22.5% vs. SLNB: 6.0%), paraesthesia (AL: 89.8% vs. SLNB: 45.2%), and WS (AL: 50% vs. SLNB: 9.1%) ( $p:0.000$ ) (Table 2).

A multivariate analysis showed that compared to the women submitted to AL, those submitted to SLNB had a lower risk of seroma (OR=0.32; 95%CI 0.22–0.47), after adjusting for age, type of breast surgery, immediate breast reconstruction and BMI. Also, SLNB provided a protection for WI (OR=0.38; 95%CI 0.22–0.70), after adjusting for seroma and BMI (Table 3). Compared to AL, SLNB conferred a statistically significant protection against AWS, after adjusting for age, winged scapula and paraesthesia (OR=0.37; 95%CI 0.21–0.63). Similarly, it was observed a significant protection against paraesthesia,

**Table 2.** Incidence of the early postoperative complications of the cohort of women with breast cancer (T1-2N0M0) according to the axillary approach.

Variables	N total (%)	Axillary Surgery N (%)		$\chi^2$ p-value
		SLNB	AL	
<b>Wound Infection</b>				
No	870 (93.8)	654 (96.2)	216 (87.1)	0.000
Yes	58 (6.2)	26 (3.8)	32 (12.9)	
<b>Seroma</b>				
No	562 (60.6)	486 (71.5)	76 (30.6)	0.000
Yes	366 (39.4)	194 (28.5)	172 (69.4)	
<b>Axillary Web Syndrome</b>				
No	764 (89.3)	575 (94.0)	189 (77.5)	0.000
Yes	92 (10.7)	37 (6.0)	55 (22.5)	
<b>Paraesthesia</b>				
No	356 (42.3)	332 (54.8)	24 (10.2)	0.000
Yes	486 (57.7)	274 (45.2)	212 (89.8)	
<b>Winged Scapula</b>				
No	672 (79.3)	552 (90.9)	120 (50.0)	0.000
Yes	175 (20.7)	55 (9.1)	120 (50.0)	

\*The difference in sample size corresponds to the absence of information; SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy.

regardless of age and type of breast surgery (OR=0.10; 95%CI 0.06–0.16). Likewise, the SLNB conferred a statistically significant protection for the WS (OR=0.12; 95%CI 0.08–0.18), regardless of the type of breast surgery and the presence of AWS (Table 3). Crude analyses are presented in supplementary material.

## DISCUSSION

Considering the 933 women diagnosed with early staging breast cancer, treated at HCIII/INCA from 2007 to 2009, the incidence of wound complication was statistically lower among women submitted to SLNB compared to those who underwent AL. Such findings corroborate with the literature, suggesting an incidence of surgical WI in SLNB from 0.9 to 10.0%, and in women with AL this incidence varies from 3.0 to 17.0<sup>17-21</sup>. Although the incidence of seroma in women submitted to SLNB (28.5%) was significantly lower compared to AL (69.4%), it was higher than those observed in European, American and Brazilian studies. In these cases, the incidence of seroma ranged from 1.8 to 14.0% in women submitted to SLNB, whereas in those submitted to AL, it ranged from 7.6 to 32.0%<sup>14,17-21</sup>. Compared to the estimates observed in the literature, the high seroma incidence in the women of the

**Table 3.** Crude and adjusted odds ratios of early postoperative complications in women with breast cancer (T1-2N0M0) according to the axillary approach.

Variables	Crude Analysis		Adjusted Analysis*	
	OR	95%CI	OR	95%CI
<b>Seroma</b>				
AL (SLNB+AL and AL)	1		1	
SLNB	0.18	0.13–0.24	0.32	0.22–0.47
<b>Wound Infection</b>				
AL (SLNB+AL and AL)	1		1	
SLNB	0.27	0.16–0.46	0.38	0.22–0.70
<b>Axillary Web Syndrome</b>				
AL (SLNB+AL and AL)	1		1	
SLNB	0.22	0.14–0.35	0.37	0.21–0.63
<b>Paraesthesia</b>				
AL (SLNB+AL and AL)	1		1	
SLNB	0.09	0.06–0.15	0.10	0.06–0.16
<b>Winged Scapula</b>				
AL (SLNB+AL and AL)	1		1	
SLNB	0.10	0.07–0.14	0.12	0.08–0.18

SLNB: sentinel lymph node biopsy; AL: axillary lymphadenectomy; OR: odds ratio; CI: confidence interval; \*seroma: adjusted for age, wound infection, type of breast surgery, immediate breast reconstruction and BMI; \*wound infection: seroma and BMI; \*axillary web syndrome: age, winged scapula and paraesthesia; \*paraesthesia: age and type of breast surgery; \*winged scapula: type of breast surgery and axillary web syndrome.

present study could be due to differences on the seroma definition over the studies. The criteria for seroma diagnosis adopted by such studies included only seroma observed in the axilla, while in the present study it included seroma as the axilla only, as those observed in breast or plastron<sup>17-21</sup>.

Reduced risk of seroma and surgical wound infection observed for SLNB were found in a meta-analysis conducted in China<sup>8</sup>, USA<sup>3</sup> and Austria<sup>7</sup>, as compared to AL. Kell et al.<sup>3</sup> suggest a lower risk of surgical wound infection (OR=0.58; 95%CI 0.42–0.80) and seroma (OR 0.40; 95%CI 0.31–0.51) in women treated with SLNB alone, compared to those submitted to AL. A smaller incision and less extension in the dissection and rupture of lymphatic tissue related<sup>3</sup> to SLNB approach could explain the lower risk of infection and seroma.

Also, this study showed that women submitted to SLNB presented a significantly lower frequency of postoperative complications in the upper limb and scapular region homolateral to the surgery when compared to women submitted to AL. Although the physiopathology of AWS is still not well established, studies have suggested a lymphovenous damage, hypercoagulation, superficial venous and lymphatic stasis as well as disorders and lesions of tissues as result of rupture of superficial lymphatic and blood vessels during axillary surgery. It is likely that SLNB promotes a lower risk because it removes a small number of lymph nodes, reducing the injury of the collectors and axillary lymph capillaries<sup>22</sup>.

In a study conducted in Rio de Janeiro, 193 women diagnosed with breast cancer from September 2008 to June 2009 were included. A lower incidence of AWS was observed among women submitted to SLNB (11.7%) when compared to those who performed AL (36%) at 45 days after surgery. The authors observed a 68% reduction in the risk of AWS among those who underwent SLNB as compared to AL<sup>15</sup>. A similar result was observed in another study conducted at the same institution with a population of 203 women also evaluated at 45 days (SLNB=4%, AL=24%,  $p<0.001$ ) and 6 months (SLNB=2%, AL=16%,  $p<0.002$ )<sup>14</sup>.

In all published studies so far, the frequency of AWS was statistically lower among women who underwent SLNB (ranging from 0.9% to 20%), compared to those who were treated with AL (ranging from 5.2 to 72%)<sup>18,23,24</sup>. Comparing to the literature, the low incidence of AWS observed in the present study points out to the quality of the physiotherapy service of HCIII/INCA, which performs evaluations and produces guidelines for the prevention of postoperative complications before surgical treatment and postoperative follow-up<sup>25</sup>.

A great divergence still exists concerning the incidence of sensorial disorders in patients submitted to the surgical treatment of breast cancer. Cohort studies and some randomized studies found an estimated incidence of altered sensitivity ranging from 2 to 23% for SLNB and 23.3 to 85% for AL<sup>17,26,27</sup>.

Fabro et al.<sup>13</sup> developed a cohort study to evaluate pain syndrome after surgical treatment for breast cancer with patients who underwent SLNB or AL. The authors found that in the first evaluation 61.3% patients had altered touch sensitivity in the internal region of the arm. In addition, young women (<40 years) and those submitted to AL (more than 15 lymph nodes removed) showed a significant increased risk of painful syndromes, defined by the presence of the perception of hyperesthesia in the internal region of the arm or axilla. The great variability in the incidence could be explained by the variation in the method of measurement and classification of this complication (subjective and/or objective assessment), and the time length between surgery and first evaluation.

Two meta-analysis performed by Kell et al.<sup>3</sup> and Li et al.<sup>8</sup> observed a 75 and 74% reduction in the risk of sensory disorders, respectively, for patients submitted to SLNB only compared to women who received AL. Similarly, in our study, SLNB conferred a 90% reduction in the risk of sensitivity change, even after adjusting by age and type of breast surgery. Although the risk reduction is 15% different between the present study and two meta-analysis<sup>3,8</sup>, we observed an effective protection for sensorial disorders promoted by the SLNB approach.

There are few studies in Brazil and worldwide comparing the incidence of WS in women submitted to SLNB and AL. However, in all of them the WS was more frequent in women submitted to AL. Paim et al.<sup>12</sup> conducted in Brazil a study with 96 patients, and observed a higher WS incidence (8.4%) in patients who underwent AL than in women submitted to SLNB (0%). At a randomized clinical trial conducted by Adriaenssens et al.<sup>28</sup>, greater WS incidence was seen on AL (21.3%), as compared to SLNB only (4.2%). Also, AL was strongly associated with the WS conferring a 10.6-fold risk of WS, regardless of age and BMI, when compared to SLNB. A prospective cohort study conducted in Brazil<sup>16</sup> found a higher incidence in women submitted to AL (22.6%) when compared to those receiving SLNB only (2.9%) after 15 days postoperative ( $p<0.01$ ).

Studies that included only women submitted to AL found incidences ranging from 27<sup>9</sup> to 73.3%<sup>10</sup>. Divergence between results may be due to a small sample size of those studies, as well as a time length after surgery ranging from the immediate postoperative period up to 12 months<sup>9-11,29</sup>. In addition, WS is a condition diagnosed by clinical observation and there are different clinical tests for assessment<sup>10</sup>. Thus, different WS incidence estimates may arise depending on the clinical tests and criteria used to assessment. Compared to patients submitted to AL, we found an 88% reduction in the risk of WS for patients who underwent SLNB, adjusted by type of breast surgery and AWS. This protection conferred by the SLNB could be explained by the fact that this surgery allows the resection of a smaller number of lymph nodes and preserve the long thoracic nerve, avoiding the anterior serratus muscle deficiency<sup>30</sup>.



The present study was the first Brazilian study to evaluate the effect of the axillary approach on the incidence of all major early postoperative complications in women with breast cancer, controlling for the effect of complications of each other. Plus, it has the advantage of including the largest number of patients among all Brazilian studies related to early postoperative complications, reducing type-II error. However, there are also limitations that should be considered, such as those inherent in retrospective studies. Collecting data based on medical, physiotherapy, and nursing records could introduce limitations related to the data quality obtained in the routine appointments. However, in the HCIII/INCA those health care services have standardized

protocols and a team specialized aiming to promote interventions for prevention of such complications.

## CONCLUSION

The present study suggests that the SLNB significantly reduced the risk of early surgical complications such as infection, seroma, AWS, paraesthesia and WS, even after adjusted by age, BMI, type of breast surgery and other related complications. However, although the SLNB technique promotes a protective effect, it still presents some risk complications, which should be a focus of prevention, management and follow-up.


## REFERENCES

1. 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 No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [cited on June 5, 2017]. Available from: <http://globocan.iarc.fr>
2. Abrahão KS, Bergmann A, Aguiar SS, Thuler LCS. Determinants of advanced stage presentation of breast cancer in 87,969 Brazilian women. *Maturitas*. 2015;82:365-70. <https://doi.org/10.1016/j.maturitas.2015.07.021>
3. Kell MR, Burke JP, Barry M, Morrow M. Outcome of axillary staging in early breast cancer: a meta-analysis. *Breast Cancer Res Treat*. 2010;120(2):441-7. <https://doi.org/10.1007/s10549-009-0705-6>
4. Lyman GH, Temin S, Edge SB, Newman LA, Turner RR, Weaver DL, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2014;32(13):1365-83. <https://doi.org/10.1200/JCO.2016.71.0947>
5. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. NCCN Guidelines Insights: Breast Cancer, Version 1.2017. *J Natl Compr Cancer Netw*. 2017;15(4):433-51.
6. Verbelen H, Gebruers N, Eeckhout FM, Verlinden K, Tjalma W. Shoulder and arm morbidity in sentinel node-negative breast cancer patients: a systematic review. *Breast Cancer Res Treat*. 2014;144:21-31. <https://doi.org/10.1007/s10549-014-2846-5>
7. Glechner A, Wöckel A, Gartlehner G, Thaler K, Strobelberger M, Griebler U, et al. Sentinel lymph node dissection only versus complete axillary lymph node dissection in early invasive breast cancer: a systematic review and meta-analysis. *Eur J Cancer*. 2013 Mar;49(4):812-25. <https://doi.org/10.1016/j.ejca.2012.09.010>
8. Li CZ, Zhang P, Li RW, Wu CT, Zhang XP, Zhu HC. Axillary lymph node dissection versus sentinel lymph node biopsy alone for early breast cancer with sentinel node metastasis: A meta-analysis. *Eur J Surg Oncol*. 2015;41(8):958-66. <https://doi.org/10.1016/j.ejso.2015.05.007>
9. Pereira TB, Bergmann A, Ribeiro ACP, da Silva JG, Dias R, Ribeiro MJP, et al. Myoelectric activity pattern of scapular muscles after axillary lymphadenectomy in breast cancer. *Rev Bras Ginecol Obstet*. 2009;31(5):224-9.
10. Oliveira JF, Bezerra T, Ribeiro ACP, Dias RA, Abrahão F, Silva JG, et al. Incidence and risk factors of winged scapula after axillary lymph node dissection in breast cancer surgery. *Appl Can Res*. 2009;29(2):69-73.
11. Mastrella AS, Freitas-Junior R, Paulinelli RR, Soares LR. Incidence and risk factors for winged scapula after surgical treatment for breast cancer. *J Clin Nurs*. 2014;23(17-18):2525-31. <https://doi.org/10.1111/jocn.12443>
12. Paim CR, de Paula Lima ED, Fu MR, de Paula Lima A, Cassali GD. Post Lymphadenectomy complications and quality of life among breast cancer patients in Brazil. *Cancer Nurs*. 2008;31:302-9. <https://doi.org/10.1097/01.NCC.0000305747.49205.b1>
13. Fabro EAN, Bergmann A, Silva BA, Ribeiro ACP, Abrahão KS, Ferreira MGCL, et al. Post-mastectomy pain syndrome: Incidence and risks. *The Breast*. 2012;21(3):321-5. <https://doi.org/10.1016/j.breast.2012.01.019>
14. Bello MA, Bergmann A, Dias RA, Thuler LCS, Tonello F, Pinto RR, et al. Incidence complications following sentinel lymph node biopsy or axillary lymph node dissection after breast cancer surgery. *J Clin Oncol*. 2012;30(27 suppl.):97. [https://doi.org/10.1200/jco.2012.30.27\\_suppl.97](https://doi.org/10.1200/jco.2012.30.27_suppl.97)
15. Bergmann A, Mendes VV, Dias RA, Silva BA, Ferreira MGCL, Fabro EAN. Incidence and risk factors for axillary web syndrome after breast cancer surgery. *Breast Cancer Res Treat*. 2012;131(3):987-92. <https://doi.org/10.1007/s10549-011-1805-7>
16. Rizzi SK, Haddad CA, Giron PS, Pinheiro TL, Nazário AC, Facina G. Winged scapula incidence and upper limb morbidity after surgery for breast cancer with axillary dissection. *Support Care Cancer*. 2016;24(6):2707-15. <https://doi.org/10.1007/s00520-016-3086-5>
17. Langer I, Guller U, Berclaz G, Koechli OR, Schaer G, Fehr MK, et al. Morbidity of Sentinel Lymph Node Biopsy (SLN) Alone Versus SLN and Completion Axillary Lymph Node Dissection After Breast Cancer Surgery: a Prospective Swiss Multicenter Study on 659 Patients *Annals of Surgery*. *Ann Surg*. 2007;245(3):452-61. <https://dx.doi.org/10.1097%2F01.sla.0000245472.47748.ec>

18. Wernicke AG, Shamis M, Sidhu KK, Turner BC, Goltser Y, Khan I, et al. Complication rates in patients with negative axillary nodes 10 Years after local breast radiotherapy following either sentinel lymph node dissection or axillary clearance. *Am J Clin Oncol*. 2013;36(1):12-9. <https://doi.org/10.1097/COC.0b013e3182354bda>
19. Rietman JS, Dijkstra PU, Geertzen JHB, Baas P, Vries J, Dolsma W, et al. Short-Term Morbidity of the Upper Limb after Sentinel Lymph Node Biopsy or Axillary Lymph Node Dissection for Stage I or II Breast Carcinoma. *Cancer*. 2003;98:690-6. <https://doi.org/10.1002/cncr.11545>
20. Lucci A, McCall LM, Beitsch PD, Whitworth PW, Reintgen DS, Blumencranz PW, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol*. 2007;25(24):3657-63. <https://doi.org/10.1200/JCO.2006.07.4062>
21. Crane-Okada R, Wascher RA, Elashoff D, Giuliano AE. Long-term morbidity of sentinel node biopsy versus complete axillary dissection for unilateral breast cancer. *Ann Surg Oncol*. 2008;15(7):1996-2005. <https://doi.org/10.1245/s10434-008-9909-y>
22. Yeung WM, McPhail SM, Kuys SS. A systematic review of axillary web syndrome (AWS). *J Cancer Surviv*. 2015;9(4):576-98. <https://doi.org/10.1007/s11764-015-0435-1>
23. Leidenius M, Leppanem E, Krogerus L, von Smitten K. Motion restriction and axillary web syndrome after sentinel node biopsy and axillary clearance in breast cancer. *Am J Surg*. 2003;185(2):127-30.
24. Lacomba MT, Mayoral del Moral O, Zazo JLC, Sánchez MJY, Ferrandez JC, Goñi AZ. Axillary web syndrome after axillary dissection in breast cancer: a prospective study. *Breast Cancer Res Treat*. 2009;117:625-30. <https://doi.org/10.1007/s10549-009-0371-8>
25. Bergmann A, Ribeiro MJP, Pedrosa E, Nogueira EA, Oliveira ACG. Physical Therapy in Breast Cancer: clinical protocol at the Cancer Hospital III/INCA. *Rev Bras Cancerol*. 2006;52(1):97-109.
26. Veronesi U, Paganelli G, Viale G, Luini A, Zurrada 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(6):546-53. <https://doi.org/10.1056/NEJMoa012782>
27. Aerts PD, De Vries J, Vander Steeg AF, Roukema JA. The relationship between morbidity after axillary and long-term quality of life in breast cancer patients: The role of anxiety. *Eur J Surg Oncol*. 2011;37(4):344-9. <https://doi.org/10.1016/j.ejso.2011.01.016>
28. Adriaenssens N, De Ridder M, Lievens P, Parijs HV, Vanhoeij M, Miedema G, et al. Scapula alata in early breast cancer patients enrolled in a randomized clinical trial of post-surgery shortcourse image-guided radiotherapy. *World J Surg Oncol*. 2012;10:86. <https://doi.org/10.1186/1477-7819-10-86>
29. Teixeira LFN, Lohsiriwat V, Schorr MC, Luini A, Galimberti V, Rietjens M, et al. Incidence, predictive factors, and prognosis for winged scapula in breast cancer patients after axillary dissection. *Support Care Cancer*. 2014;22(6):1611-7. <https://doi.org/10.1007/s00520-014-2125-3>
30. Martin RM, Fish DE. Scapular winging: anatomical review, diagnosis, and treatments. *Current Rev Musculoskelet Med*. 2008;1:1-11. <https://doi.org/10.1007/s12178-007-9000-5>

# CORRELATION OF MAMMOGRAPHIC AND HISTOPATHOLOGICAL FINDINGS IN PATIENTS SUBMITTED TO MAMMOTOMY

## Correlação de achados mamográficos e histopatológicos de pacientes submetidas a mamotomia

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### ABSTRACT

**Objective:** To correlate patients with BI-RADS 4 or 5 mammographic results submitted to mammotomy and compare these findings to histopathological ones. **Method:** We selected 111 patients with non-palpable breast lesions detected on mammography and who underwent mammotomy at Clínica de Oncologia e Mastologia de Natal. The samples were sent to the laboratory Dr. Getulio Sales, after x-ray of the pieces, and all patients had to use a titanium clip. **Results:** The prevalent age group was 41-50 years (40.5%); approximately 30.6% had a family history of breast cancer; among the patients selected, 97.3% had a BI-RADS 4 classification and 2.7%, a BI-RADS 5; with microcalcifications being the main reason for mammotomy indication in both cases. The distribution of benign and malignant lesions was 70 and 30%, respectively. The prevalent malignant lesion was ductal carcinoma *in situ* (58%). Clinical suspicion of malignancy according to BI-RADS 4 and 5 was statistically significant,  $p=0.018$  [95%CI 0.28 (0.209–0.383)]. The degree of association verified through odds ratio showed that the BI-RADS 5 group had 72% less chance of having a benign lesion when compared to the BI-RADS 4 group. There were no reports of complications in patients submitted to mammotomy in the present study. **Conclusion:** Mammotomy proved to be a safe method to diagnose suspicious lesions (BI-RADS 4 and 5), and its results fit what is observed in the literature.

**KEYWORDS:** Breast cancer; early diagnosis; mammography.

### RESUMO

**Objetivo:** Correlacionar as pacientes com resultado mamográfico BI-RADS 4 ou 5 submetidas a mamotomia e comparar os achados com os encontrados na histopatologia. **Método:** Foram selecionadas 111 pacientes as quais apresentavam lesões mamárias não palpáveis detectadas na mamografia e que realizaram mamotomia na Clínica de Oncologia e Mastologia de Natal. As amostras foram enviadas para o laboratório Dr. Getulio Sales, após radiografia das peças, e todas as pacientes tiveram de colocar clipe de titânio. **Resultados:** A faixa etária predominante foi de 41–50 anos (40,5%); cerca de 30,6% possuía histórico familiar de câncer de mama; entre as selecionadas, 97,3% possuíam classificação 4 do BI-RADS e 2,7% tinham classificação 5, predominando, em ambos os casos, as microcalcificações como indicação de mamotomia. A distribuição entre lesões benignas e malignas foi de 70 e 30%, respectivamente. A prevalência de lesões malignas foi de carcinoma ductal *in situ* (58%). Houve significância estatística com relação à suspeição de malignidade de acordo com o BI-RADS 4 e 5,  $p=0,018$  [IC95%0,28 (0,209–0,383)]. O grau de associação verificado por meio da odds ratio mostra que o grupo BI-RADS 5 tinha 72% menos chance de ser benigno quando comparado ao grupo BI-RADS 4. Não houve relato de complicações nas pacientes submetidas a mamotomia no presente estudo. **Conclusão:** A mamotomia mostrou-se um método seguro no diagnóstico de lesões suspeitas (BI-RADS 4 e 5), estando dentro do observado na literatura.

**PALAVRAS-CHAVE:** Câncer de mama; diagnóstico precoce; mamografia.

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## INTRODUCTION

Breast cancer is one of the main public health issues worldwide, and its incidence significantly increased in recent decades. According to a World Health Organization publication<sup>1</sup>, breast cancer is the second most common type of malignant neoplasm among women in the world.

Mammography is an excellent early screening method for breast cancer, and, according to several studies, it results in a decrease in mortality, with a gain in overall survival<sup>2</sup>.

Patients with BI-RADS 4 and 5 mammographic abnormalities receive an indication to incisional biopsy. These lesions have a higher suspicion of malignancy but do not always need a surgical procedure. However, diagnostic investigation through an invasive procedure with tissue removal and histopathological study is mandatory<sup>3</sup>.

According to Hall, non-palpable lesions subjected to surgical biopsy have a malignancy rate of 15–30%, and mammographic screening has contributed to increasing the number of unnecessary procedures<sup>4</sup>. In this scenario, we can conclude that most surgeries could be avoided with regular patient follow-up.

Thus, percutaneous biopsy emerged as an alternative to surgical biopsy for diagnostic clarification of categories 4 and 5, providing a better cost-benefit ratio, shorter procedure time, greater comfort to the patient, and lower risk of complications, in addition to a smaller scar in the radiological follow-up examinations<sup>5</sup>.

Vacuum-assisted percutaneous biopsy, also known as mammotomy, is a technique that can remove the entire lesion seen on mammography or ultrasound with a single needle insertion into the breast, extracting a larger volume of breast tissue and surpassing the core biopsy and Fine-Needle Aspiration. Stereotactic mammotomy has greater benefits, mainly in microcalcification removal<sup>6</sup>.

According to Crippa, in a study performed with patients undergoing both ultrasound-guided and mammography-guided mammotomy, it was possible to demonstrate that the method was effective for histopathological study and precise in obtaining the necessary material<sup>7</sup>. A study with 397 patients submitted to ultrasound-guided mammotomy proved that the method was safe and had good accuracy, with a sensitivity of 97.4% and specificity of 100%<sup>8</sup>.

Considering the need for a histological study with a group of patients with suspicious lesions (BI-RADS 4 and 5), our goal was to correlate the mammography radiological findings and compare them to histopathological results after removing these lesions with mammotomy.

## METHOD

This is a cross-sectional, retrospective study based on the findings of histopathological results of women who underwent mammotomy at Clínica de Oncologia e Mastologia de Natal, the only institution that performed this procedure

during the study period — from January 2010 to June 2015. We analyzed the following data: age, BI-RADS, distribution and morphology of mammographic findings, presence of benign or malignant lesions in the histopathological study and their distribution, family history of breast cancer, age at first pregnancy and menarche.

The sample consisted of patients with suspicious mammographic findings (BI-RADS 4 and 5) who underwent mammotomy in the location of the study. The exclusion criteria were lack of knowledge of referral to the procedure and lack of histopathological report.

Data were collected directly from the patients' medical records and pathology report, through a form elaborated by the researchers involved in the study, from January 2010 to June 2015. The collection occurred in the Medical Archive of Clínica de Oncologia e Mastologia de Natal, during the hours of operation.

The collected data were recorded in an encoded Microsoft Excel table, accessible with a password known only by the researchers. Subsequently, we analyzed the results using the software Statistical Package for Social Sciences (SPSS version 14.0). The variables were subjected to the  $\chi^2$  test. We considered significant all tests with  $p < 0.05$ . Patients were identified by numbers on the data collection form to ensure that only the researchers involved had knowledge of and access to the information.

## RESULTS

### Clinical-epidemiological profile of the sample

Initially, we assessed 196 patients submitted to a diagnostic procedure, dismissing 85 for not having mammographic information and/or pathology report in their medical record. The remaining 111 patients underwent statistical analysis.

The prevalent age group was 40–50 years, which was expected due to the high demand for screening among these patients, resulting in a higher number of suspicious findings and diagnostic procedures (Graphic 1). Sixty-four percent of the patients breastfed their children for any period (Graphic 2). Less than half (30.6%) had a history of some relative with breast cancer (Graphic 3).

A large portion of patients with non-palpable lesions belonged to the age group 41–60 years, with a slight prevalence of the range 41–50 years. This result suggests the importance of screening the target population starting at 40 years of age to detect suspicious lesions early and, consequently, cancer cases still in their initial stages.

The findings of non-palpable lesions occurred predominantly in the UOQ of the left breast, followed by the UOQ of the right breast, and together they reached 63% of the cases (Table 1).

Almost all patients were in category 4 of BI-RADS, with only a few in category 5. Three patients were in category 0 for having dense breasts. However, it was possible to outline the lesions seen

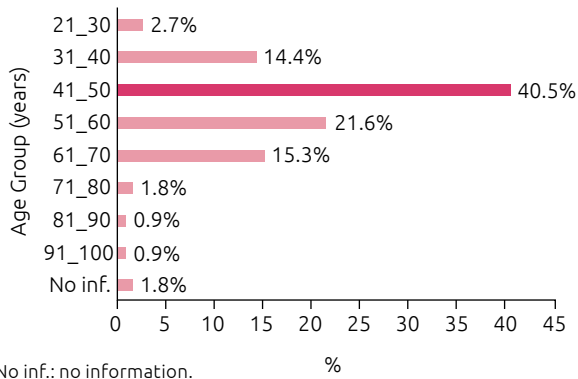
in mammography, and after reassessing the images, they were considered BI-RADS 4 (Graphic 4 and Table 2).

Microcalcifications were the main cause of mammotomy indications, followed by architectural distortions (Table 3).

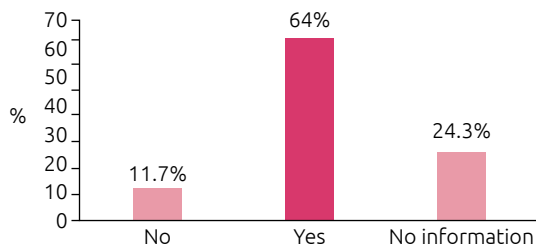
Architectural distortions associated with microcalcifications classified as BI-RADS 5 had linear microcalcifications, following a ductal path (Table 4).

All BI-RADS 5 patients had a histopathological diagnosis of category 4 carcinoma; only 28.3% of them were cancer (Tables 5 and 6 and Graphic 5).

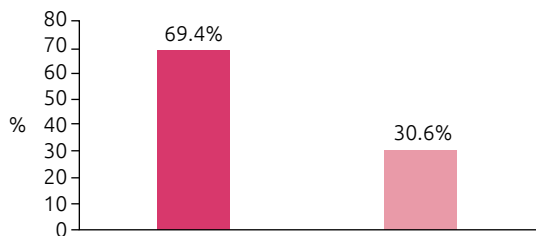
There were 33 cases (29.7%) of malignant lesions, with a prevalence of carcinoma *in situ*, corroborating that the mammographic findings contributed to the early detection of breast cancer (Table 7 and Graphic 6).



Graphic 1. Patient characteristics.



Graphic 2. Patient characteristics: breastfed.



Graphic 3. Patient characteristics: cancer history.

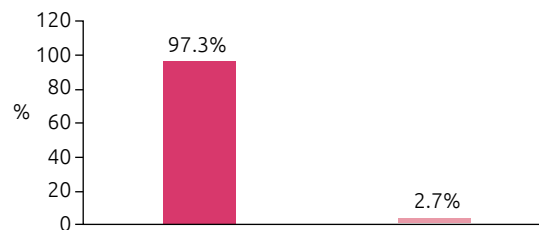
## DESCRIPTION OF THE STATISTICAL ANALYSIS

The tabulation and exploratory data analysis were conducted based on descriptive statistics, using tables and measures to summarize the data for a better interpretation and

Table 1. Lesion distribution according to location.

Location	No. of patients	%
LUOQ	42	37.8
RUOQ	28	25.2
JRUQ	10	9.0
RRAR	6	5.4
JROQ	5	4.5
JRUQ+LUQ	4	3.6
RUOIQ	4	3.6
JRIQ	3	2.7
JLUQ	3	2.7
JLLQ	2	1.8
RLOQ	1	0.9
LLOQ	1	0.9
LLIQ	1	0.9
RUIQ	1	0.9
Total	111	100.0

LUOQ: left upper outer quadrant; RUOQ: right upper outer quadrant; JRUQ: junction of the right upper quadrants; RRAR: right retroareolar region; JROQ: junction of the right outer quadrants; JRUQ+LUQ: junction of the right upper quadrant and left upper quadrant; RUOIQ: right upper outer-inner quadrant; JRIQ: junction of the right inner quadrants; JLUQ: junction of the left upper quadrants; JLLQ: junction of the left lower quadrants; RLOQ: right lower outer quadrant; LLOQ: left lower outer quadrant; LLIQ: left lower inner quadrant; RUIQ: right upper inner quadrant.



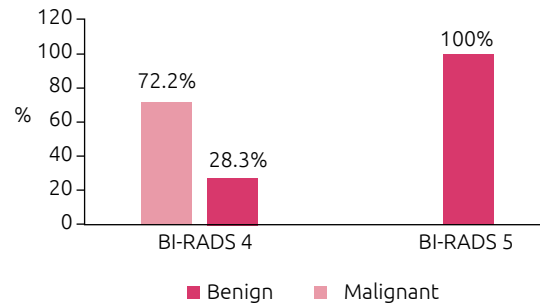
Graphic 4. Distribution according to the Breast Imaging-Reporting and Data System (BI-RADS).

Table 2. Distribution according to the Breast Imaging-Reporting and Data System (BI-RADS).

BI-RADS	Amount	%
4	108	97.3
5	3	2.7
Total	111	100.0

**Table 3.** Distribution according to mammotomy (MMT) indication.

MMT Indication	Amount	%
Microcalcifications	91	82
Architectural distortion	1	0.9
Focal asymmetry with microcalcifications	5	4.5
Calcifications	4	3.6
Focal asymmetry	1	0.9
Focal asymmetry with isolated calcification	1	0.9
Nodule with microcalcifications	1	0.9
Architectural distortion with microcalcifications	7	6.3
Irregular nodule	1	0.9
Total	111	100.0



**Graphic 5.** Distribution of Breast Imaging-Reporting and Data System (BI-RADS) according to benign and malignant diseases.

**Table 4.** Distribution according to Mammotomy (MMT) indication and Breast Imaging-Reporting and Data System (BI-RADS).

MMT Indication	BI-RADS		Gran
	4	5	Total
Microcalcifications	91	-	91
Architectural distortion associated with microcalcifications	4	3	7
Focal asymmetry with microcalcifications	5	-	5
Calcifications	4	-	4
Focal asymmetry	1	-	1
Focal asymmetry with isolated calcification	1	-	1
Nodule with microcalcifications	1	-	1
Architectural distortion	1	-	1
Total	106	3	111

**Table 5.** Comparison between mammography findings and histopathological classification.

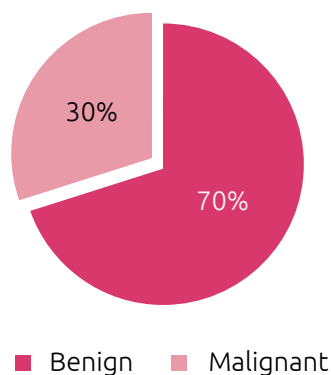
MMT Indication	Classification			
	Benign	(%)	Malignant	(%)
Focal asymmetry (N=1)	1	100.0	-	0.0
Focal asymmetry with isolated calcification (N=1)	1	100.0	-	0.0
Focal asymmetry with microcalcifications (N=6)	3	50.0	3	50.0
Nodule with microcalcifications (N=1)	1	100.0	-	0.0
Architectural distortion associated with microcalcifications (N=7)	1	14.3	6	85.7
Microcalcifications (N=91)	66	74.2	24	25.8
Architectural distortion (N=1)	1	100.0	-	0.0

**Table 6.** Distribution of Breast Imaging-Reporting and Data System (BI-RADS) according to benign and malignant diseases.

BI-RADS	Benign	%	Malignant	%	Grand Total
4	78	71.7	30	28.3	108
5	0	0.0	3	100.0	3
Total	78	-	33	-	111

**Table 7.** Distribution of histopathological diagnosis.

Diagnosis	Lesions	%
Benign (N=78)		
Dystrophic calcification	64	82.1
Dystrophic microcalcifications	5	6.4
Fibroadenoma	2	2.6
Fibrosis	2	2.6
Sclerosing Adenosis	1	1.3
Microscopic cyst	1	1.3
Fibroadenoma with calcifications	1	1.3
Usual ductal hyperplasia (UDH)	1	1.3
Stromal microcalcifications	1	1.3
Malignant (N=33)		
High grade ductal carcinoma <i>in situ</i>	13	39.4
Invasive ductal carcinoma G3	5	15.2
Invasive ductal carcinoma G2	3	9.1
Intermediate grade ductal carcinoma <i>in situ</i>	4	12.1
Lobular carcinoma <i>in situ</i>	2	6.0
Invasive ductal carcinoma G1	2	6.0
Invasive ductal carcinoma G2 + High grade ductal carcinoma <i>in situ</i>	1	3.0
Invasive lobular carcinoma G2	1	3.0
Invasive ductal carcinoma G2 + Low grade ductal carcinoma <i>in situ</i>	1	3.0
Invasive ductal carcinoma G2 + Intermediate grade ductal carcinoma <i>in situ</i>	1	3.0
Total	111	-

**Graphic 6.** Percentage of benign x malignant histopathological findings.

presentation of results. We used the software Microsoft Excel to analyze the data, and SPSS 20 for Windows (IBM, USA) to perform the  $\chi^2$  statistical test, at a significance level of 5%, in order to assess whether an association between the variables existed. The degree of association was verified through odds ratio.

### Test of association between variables

To evaluate if there was an association between the variables “BI-RADS” and “condition (benign or malignant),” we conducted the  $\chi^2$  statistical test, with a significance level of 5%. We can confirm that the association between BI-RADS and condition (benign or malignant) was significant,  $p=0.018$ . The degree of association verified through odds ratio showed that the BI-RADS 5 group had 72% less chance of having a benign lesion when compared to the BI-RADS 4 group (Table 8).

## DISCUSSION

The early diagnosis of breast cancer has been one of the greatest allies in its treatment. Periodic mammography with screening indication for women aged 40 years and older has become the main form of detection of suspicious lesions in the early stages of cancer, especially suspicious microcalcifications. However, this method fails to diagnose approximately 10–30% of cancer cases. The age group of patients was wide, ranging from 21 to 90 years.

The patients submitted to this procedure were mostly 40- to 50-year-olds, indicating that finding non-palpable lesions at this age can aid in the early diagnosis of breast neoplasms. All patients underwent stereotactic mammotomy. Less than half of the patients (30.6%) had a family history of breast cancer, confirming that the study included a heterogeneous sample, consistent with what we usually see in a screening population. Over half of the lesions were in the upper quadrants (63%), which can be justified by the greater volume of breast tissue in this location.

According to mammographic findings, the vast majority of patients belonged to the group of category 4 lesions (97.3%), with microcalcifications as one of the main causes of indication. At first, some tests classified as category 3 and 0 received a mammotomy indication, with a reassessment of the lesions and reclassification as category 4.

**Table 8.** Association between variables.

BI-RADS	Benign (%)	Malignant (%)	OR (95%CI)	P
4	71.7 (76)	28.3 (30)	0.28 (0.209–0.383)	0.018
5	0 (0)	100 (3)		

BI-RADS: Breast Imaging-Reporting and Data System; OR: odds ratio; 95%CI: confidence interval of 95%.

Our study identified that microcalcifications had the higher number of mammotomy indications (80.2%). In a study conducted by Tonegutti et al.<sup>9</sup>, microcalcifications represented 77.5% of indications for patients who underwent mammotomy. According to Chagas et al.<sup>10</sup>, suspicious microcalcifications are associated with 20–30% of cases of carcinoma in general, both *in situ* and invasive. Chala and Shimizu<sup>2</sup> consider microcalcifications one of the most important signs of non-palpable breast cancer, detected almost exclusively by mammography, with a high probability of ductal carcinoma *in situ*. In the present study, we found a value of 28%, which is in agreement with the literature.

The other malignant lesions were focal asymmetry associated with microcalcifications (50% were malignant) and architectural distortion associated with microcalcifications (85.7% were malignant). Thus, we can affirm that these findings had a higher degree of suspicion for histopathological diagnosis of malignancy.

Asymmetries can be the initial findings of a tumor before it progresses to a nodule. They represent an area of fibroglandular tissue, which is larger in one breast when compared to the contralateral one. Focal asymmetries are restricted to a small area of the breast, occupying less than one quadrant, and have a higher degree of suspicion of malignancy. When associated with another finding, such as microcalcifications, the final classification is the one of the more suspicious finding (BI-RADS 4)<sup>3</sup>. In our study, focal asymmetries associated with suspicious microcalcifications had a high rate of malignancy: three cases of carcinoma out of six.

Architectural distortions, when not associated with trauma, surgery history, or inflammatory process, are considered suspicious and require diagnostic investigation. They represent 5–10% of non-palpable carcinomas detected on mammography screening<sup>10</sup>. In the present study, this value was far from the aforementioned since only one patient had just architectural distortion, and the histopathological diagnosis was benign. However, when associated with microcalcifications, the incidence of malignancy was 85.5%. The cases of architectural distortion with linear microcalcifications were radiologically classified as BI-RADS 5.

The malignant findings in patients were distributed in the following manner: 78% had carcinoma *in situ*, and the others had invasive carcinoma, which suggests that a good screening method and precise diagnostic confirmation can early detect lesions still in their initial stage. According to the literature, mammotomy has good accuracy in diagnosing carcinoma *in situ*, with an underestimation of less than 10% for invasive carcinoma. As our work did not aim to calculate its

accuracy, we did not compare mammotomy with other diagnostic methods.

The results of malignant findings in patients submitted to mammotomy according to the BI-RADS classification for suspicious lesions showed that among those in category 4, 30 out of 108 patients had cancer (28%), which is within the expected in the literature for a final cancer diagnosis (20–30%)<sup>2</sup>. In cases of benign diagnosis, patients can be safely monitored, decreasing costs, and avoiding the morbidity of surgery.

All three patients with lesions classified as highly suspicious (category 5) had a diagnosis of cancer, totaling 100%. Other authors have reported similar results, with the malignancy rate ranging from 85–100%<sup>6,8</sup>. In these cases, entirely removing the lesion from a radiological point of view does not mean entirely removing the neoplasm from the surgical specimen, and a complementary surgery is necessary according to pathological findings. Therefore, in this situation, other diagnostic methods with better cost-benefit ratio could be more indicated, such as the mammography-guided core biopsy.

Although there are complication reports in the literature, mainly related to bleedings and hematomas, with rates between 2 and 7%, this study had no such cases. The care methods taken were administering anesthesia with local vasoconstrictor effects, local compression, instructions for cryotherapy and use of a bra, and compression dressing for home, in addition to leaving the patient under observation for approximately one hour after the procedure.

Considering the concordance between our work and data from the literature, we can affirm that mammotomy is a suitable method to investigate suspicious lesions, especially those classified as BI-RADS 4, and is diagnostic and curative for benign lesions.

Subsequently, the study can be improved with the inclusion of histopathological findings in patients who underwent surgery to try to find whether the lesions were entirely removed, as well as the follow-up of the other patients.

## CONCLUSIONS

Mammotomy proved to be a safe and efficient method to investigate suspicious non-palpable lesions, such as those found in mammographies, having a malignancy rate within the expected according to the literature. Benign cases could be regarded as treated.

Among the malignancy findings, the prevalence of lesions *in situ* favors the early diagnosis of breast cancer, allowing a higher chance of cure and reconstructive surgeries.



## REFERENCES

1. Stewart BW, Wild CP. World Cancer Report. World Health Organization; 2014.
2. Chala LF, Shimizu CCP. Rastreamento mamográfico na população em geral. In: Frasson AL, Millen E, Brenelli F, Luzzatto F, Berrettini Jr. A, Cavalcante FP, Eds. Doenças da mama: guia prático baseado em evidências. São Paulo: Atheneu; 2011. p. 51-7.
3. American College of Radiology. ACR BI-RADS Atlas: Mammography. American College of Radiology; 2013.
4. Hall FM, Storella JM, Silverstone DZ, Wyshak G. Nonpalpable breast lesions: recommendations for biopsy based on suspicion of carcinoma at mammography. *Radiology*. 1988;167(2):353-8. <https://doi.org/10.1148/radiology.167.2.3282256>
5. Dhillon MS, Bradley SA, England DW. Mamotome biopsy: Impact on preoperative diagnosis rate. *Clin Radiol*. 2006;61(3):276-81. <https://doi.org/10.1016/j.crad.2005.08.017>
6. Ketrutz U, Morack G, Decker T. Stereotactic vacuum-assisted breast biopsies in 500 women with microcalcifications: Radiological and pathological correlations. *Eur J Radiol*. 2005;55(2):270-6. <https://doi.org/10.1016/j.ejrad.2004.10.014>
7. Crippa CG, D'Avila CLP, Schaefer MB, Oliveira, AR TE. A mamotomia no diagnóstico e terapêutica de lesões mamárias. *Femina*. 2006;34(10):687-93.
8. Urban LABD, Cianfarano A, Cassano E, Pizzamiglio M, Renne G, Bellomi M. Biópsia percutânea a vácuo (mamotomia) guiada por ultra-sonografia: experiência de 404 casos. *Radiol Bras*. 2005;39(Supl. 2):1-98.
9. Tonegutti M, Girardi V. Stereotactic vacuum-assisted breast biopsy in 268 nonpalpable lesions Biopsia mammaria in stereotassi, vacuum-assisted, in 268 lesioni non palpabili. *Radiologia Medica*. 2008;113(1):65-75. <https://doi.org/10.1007/s11547-008-0226-0>
10. Chagas CR, Menke CH, Vieira RJS, Boff RA. Tratado de Mastologia da SBM. Rio de Janeiro: Thieme Revinter; 2011.

# NUTRITIONAL PROFILE AND ITS CORRELATION WITH THE MAIN PROGNOSTIC FACTORS IN WOMEN WITH BREAST CANCER UNDERGOING SURGICAL TREATMENT

Perfil nutricional e sua correlação com os principais fatores prognósticos em mulheres com câncer de mama submetidas a tratamento cirúrgico

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## ABSTRACT

**Objective:** To analyze the association of nutritional status and fasting blood glucose with the main tumor prognostic factors in invasive breast cancer in women undergoing surgical treatment. **Methods:** Retrospective study with women aged 18 years or older, diagnosed with invasive breast cancer, admitted for surgical treatment at Cancer Hospital III – National Cancer Institute José Alencar Gomes da Silva. The variables collected were: age, Body Mass Index (BMI), comorbidities (hypertension and diabetes mellitus), neoadjuvant chemotherapy, menopausal status, fasting blood glucose, clinical staging, and tumor markers (estrogen and progesterone receptor/HER2/Ki-67). Categorical data were expressed by frequency and percentage, and numerical data by mean and standard deviation. We used the following tests to perform the statistical analysis: Kruskal-Wallis, Mann-Whitney, Pearson's  $\chi^2$ , and Spearman tests. P-values  $<0.05$  were considered statistically significant. **Results:** 166 patients participated in the study. The mean age was 59.1 ( $\pm 12.4$ ) years, and the mean fasting blood glucose was 109.5 $\pm$ 23.7 mg/dL. According to BMI, 62.1% of the sample was overweight. The high BMI was related to hypertension and hyperglycemia, and no association with prognostic factors was found. Hyperglycemia was associated with more advanced age, higher lymph node involvement, hormone receptor positive, and post-menopausal status. **Conclusion:** The nutritional status classified by BMI was not related to prognostic factors in breast cancer, suggesting the need for other complementary anthropometric methods for better nutritional diagnosis.

**KEYWORDS:** Breast neoplasms; neoplasm staging; prognosis; nutritional status; obesity; hyperglycemia.

## RESUMO

**Objetivo:** Analisar a associação do estado nutricional e glicemia de jejum com os principais fatores prognósticos tumorais no câncer de mama invasivo em mulheres submetidas a tratamento cirúrgico. **Métodos:** Estudo retrospectivo com mulheres maiores de 18 anos, diagnosticadas com câncer de mama invasivo, admitidas para tratamento cirúrgico no Hospital de Câncer III — Instituto Nacional de Câncer José Alencar Gomes da Silva. As variáveis coletadas foram: idade, Índice de Massa Corporal (IMC), comorbidades (hipertensão arterial sistêmica e diabetes mellitus), quimioterapia neoadjuvante, estado menopausal, glicemia de jejum, estadiamento clínico e marcadores tumorais (Receptor de Estrogênio e Progesterona/Her-2/Ki 67). Os dados categóricos foram expressos pela frequência e percentual e os dados numéricos pela média e desvio padrão. A análise estatística foi realizada por meio dos testes de: Kruskal-Wallis, Mann-Whitney,  $\chi^2$  de Pearson e Sperman. P-valores  $<0,05$  foram considerados estatisticamente significantes. **Resultados:** 166 pacientes participaram da pesquisa. A média de idade foi de 59,1 ( $\pm 12,4$ ) anos e a média de glicemia de jejum foi 109,5 $\pm$ 23,7 mg/dL. De acordo com o IMC, 62,1% da amostra foi classificada com excesso de peso. O IMC elevado estava associado à presença de hipertensão e hiperglicemia, e não foi observada associação com fatores prognósticos. A hiperglicemia estava relacionada com idade mais avançada, maior comprometimento linfonodal, receptor hormonal positivo e estado pós-menopausal. **Conclusão:** O estado nutricional classificado pelo IMC não foi associado com fatores prognósticos no câncer de mama, sugerindo a necessidade de outros métodos antropométricos complementares para melhor diagnóstico nutricional.

**PALAVRAS-CHAVE:** Neoplasias da mama; estadiamento de neoplasias; prognóstico; estado nutricional; obesidade; hiperglicemia.

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## INTRODUCTION

Breast cancer is the most common type of cancer in women around the world, representing 25% of all cases worldwide and 29.5% in Brazil. It is the most frequent tumor among the female population in all regions of the country, except the North, and the leading cause of death by cancer in developing countries.<sup>1</sup>

Breast neoplasia is multifactorial, involving biological-endocrine factors, reproductive life, aging, family history of breast cancer, high breast tissue density (ratio between glandular and breast adipose tissues), behavior, and lifestyle. In addition, alcohol consumption, overweight, a sedentary lifestyle, and exposure to ionizing radiation are potential agents for its development. Its prevention requires lifestyle changes; approximately 30% of breast cancer cases could be avoided with the practice of regular physical activity, a healthy diet, and body weight control.<sup>1</sup>

The World Health Organization considers obesity one of the major public health problems in the world. The estimate is that, in 2025, around 2.3 billion adults will be overweight, and more than 700 million, obese. Obesity is the excessive accumulation of body fat in an individual and has multifactorial causes.<sup>2</sup> In addition to its relationship with hypertension, diabetes, and other chronic non-communicable diseases, it is associated with the development of 13 types of cancer, including post-menopause breast cancer.<sup>3</sup> Overweight and obesity in breast cancer patients are connected with a worse prognosis and clinical outcome.<sup>4</sup>

According to the International Agency for Research on Cancer (IARC), the carcinogenesis process involves biological mechanisms linked to overweight, such as hyperinsulinemia, insulin resistance, changes in the metabolism of sex hormones, positive regulation of insulin-like growth factors, chronic inflammation, changes in immune function and adipokine production, vascular growth factors produced by fat tissue, and oxidative stress.<sup>3</sup>

Some studies have indicated certain causes for a worse clinical outcome in obese breast cancer patients, such as: association with other comorbidities, more advanced stage at diagnosis, unfavorable tumor characteristics, faster growth of tumor tissue due to deficient cellular immunity, pro-inflammatory state, and hormonal influences, among them high levels of estrogen and insulin.<sup>5</sup>

Some anthropometric measures can quantify body overweight, such as Body Mass Index (BMI), calculated by dividing weight in kilograms (kg) by height in meters (m) squared, kg/m<sup>2</sup>. BMI is the most widely used method to evaluate body adiposity for being simple, practical, without cost, and a good indicator to classify obesity.<sup>6</sup>

Studies have been developed on the relationship between BMI and prognostic factors in breast cancer.<sup>7</sup> A prognostic factor is a marker associated with overall survival, and a parameter of the clinical course, involving the risk of recurrence or death. Its study allows a more specific analysis of tumor behavior according to its progression, and better development of adjuvant therapy.<sup>8</sup>

Prognostic factors in breast neoplasm are classified in consonance with the patient's condition and tumor aspects. The main prognostic factors related to tumor are: histological type, degree of differentiation, size, presence of hormone receptors and tumor markers, and lymph node involvement. Regarding the host, the prognostic factors are: age at diagnosis, family history, BMI, and nutritional status, in addition to other not well-established genetic traits.<sup>9</sup>

Tumor size associated with the condition of axillary lymph nodes are the two most important prognostic indicators of breast cancer and comprise the basis of the TNM staging, established by the Union for International Cancer Control. Tumor size is directly related to the risk of recurrence and lymph node involvement, that is, smaller tumors have a better prognosis of both overall survival and disease-free survival.<sup>10</sup>

The histological grade reflects the malignant potential of the tumor, indicating its higher or lower metastasis capacity, and, when combined with the stage of the disease, it can improve the prediction of the outcome.<sup>11</sup> Age is also an important prognostic factor in breast cancer. Despite the divergences found in several studies, most investigations highlight that patients in the age group 40-59 years have the best prognosis. On the other hand, young women (<35 years) and those with more advanced age (>75 years) have the worst prognosis.<sup>12,13</sup>

Hormone receptors (HR) are proteins that bind to circulating hormones, mediating their cellular effects. Estrogen receptors (ER) and progesterone receptors (PR) are the HR most studied in breast cancer. Approximately two-thirds of breast carcinomas are HR-positive (ER and/or PR). This positivity is highly associated with a more favorable prognosis and a better response to hormone therapy when compared to patients with HR-negative tumors.<sup>13</sup>

The Human Epidermal Growth Factor Receptor 2 (HER2) is a biomarker also used as a prognostic factor. Its overexpression is related to a greater biological aggressiveness of the tumor and resistance to some types of treatment. HER2 encodes a membrane protein of tumor cells, which makes them develop faster and increases their duplication, resulting in more aggressive tumors.<sup>14</sup>

Ki-67 is also a well-studied biomarker and known as a prognostic factor. It is a nuclear protein expressed in proliferating cells and absent in resting cells. Its use as a cell proliferation marker showed that the higher its index (%), the greater the cell proliferation and the lower the patient survival. Ki-67 can be used to divide patients into groups with good or bad prognosis.<sup>15</sup>

Studies suggest that high fasting blood glucose is also related to tumor growth and worse prognosis of breast cancer due to the association between hyperglycemia and various metabolic changes.<sup>16,17</sup>

Knowledge about the correlation between nutritional status and the main prognostic factors in breast cancer patients

provides a better understanding of the population treated and the establishment of a more effective nutritional approach. Therefore, the main objective of this study was to analyze this association in women undergoing surgical treatment at Cancer Hospital III (INCA III).

## METHODS

### Study design

Observational, cross-sectional, retrospective study with patients admitted to oncological surgery at the Mastology Center of INCA III from October to December 2016.

### Eligibility criteria

Female patients aged 18 years or older, diagnosed with invasive breast cancer and admitted to the surgical wards of INCA III for curative treatment.

### Exclusion criteria

Women undergoing late reconstruction, palliative surgery, and/or who lacked information in their hospital records.

### Data Collection

For data collection, we used Admission Forms developed by the Nutrition Service of the same institution and electronic medical records. The variables collected were:

- Age: the number of complete years from the date of birth to the date of admission. Patients over 60 years of age were classified as older adults;
- Comorbidities: systemic arterial hypertension (SAH) and diabetes mellitus (DM);
- Current clinical staging: extension of malignant neoplasm determined by the Union for International Cancer Control (UICC), through a system called TNM Classification of Malignant Tumors (tumor size, lymph node involvement, metastasis, and grade);<sup>18</sup>
- Anthropometry: weight and height measured at the time of admission and BMI classification according to the WHO<sup>2</sup> for adults and the PAHO<sup>19</sup> for older adults;
- Fasting blood glucose: verified through a biochemical test performed in the preoperative routine at INCA III. The result was collected from the electronic medical record on the day of admission. We adopted the following parameters: <100 mg/dL (normal blood glucose), 100–125 mg/dL (impaired glucose tolerance), and ≥126 mg/dL (diabetes mellitus);<sup>20</sup>
- Tumor markers: presence or absence of hormone receptors (estrogen and progesterone), and expression of HER2 and %Ki-67;
- Menopausal status: status of pre- or post-menopause reported at the time of hospitalization.

### Statistical analysis

The data collected were analyzed anonymously with the software Statistical Package for Social Sciences, version 22.0.

The description of the sample used frequency and percentage as categorical variables and mean and standard deviation as numeric variables. We used the Kruskal-Wallis and Mann-Whitney tests to compare means in two or more groups, Pearson's  $\chi^2$  test to associate two categorical variables, and Spearman's correlation coefficient to perform linear associations between two numerical variables, considered statistically significant when  $p < 0.05$ .

### Ethical aspects

The Committee for Ethics in Research (CER) of INCA III approved this study under the number CAAE 73374417.3.0000.5274.

## RESULTS

Among the 287 patients admitted, 166 were selected by the eligibility criteria of the study.

The mean age of the women under study was  $59.1 \pm 12.4$  years, ranging from 31 to 92 years, with half of the sample population consisting of older adults; 80.7% reported being in post-menopause. With respect to fasting blood glucose, 62% of the patients were in the classification above 99 mg/dL, with a mean of  $109.5 \pm 23.7$  mg/dL. Regarding anthropometric variables, the mean BMI was  $28.9 \pm 5.8$  kg/m<sup>2</sup>. Tables 1 and 2 present the sample characteristics related to clinical, anthropometric, and tumor variables.

Table 3 shows the association of mean BMI and fasting blood glucose with the main tumor prognostic factors in breast cancer. We found no association between the mean BMI and prognostic factors. Women with higher mean fasting blood glucose had a significantly more advanced age, greater lymph node involvement, progesterone and estrogen receptor positive, and were in post-menopause.

When evaluating the association between BMI categories and comorbidities, we found that most hypertensive patients were obese (51.1%) ( $p < 0.05$ ). Diabetic patients did not show this association (Table 4). Table 5 indicates that patients with higher blood glucose levels had greater mean BMI.

No significant difference was observed between the mean fasting blood glucose of patients who underwent neoadjuvant chemotherapy ( $112.7 \pm 28.6$  mg/dL) and those who did not ( $106.9 \pm 18.6$  mg/dL).

The analysis of BMI categories and prognostic factors of the entire sample showed no significant association. An analysis stratifying the sample according to menopausal status presented no significant difference between groups.

The mean Ki-67 of the total sample was  $34.1 \pm 26.1\%$ , and when correlated with BMI and fasting blood glucose, it did not show a significant relationship.

## DISCUSSION

The findings of this study related to tumor characteristics indicated that 80.7% of the patients analyzed had ER-positive tumors, similar to data presented by Anderson et al., which revealed that more than 75% of all breast cancer cases have this tumor characteristic.<sup>21</sup> The literature demonstrates that tumors with HER2 overexpression or amplification affect around 15% of patients with invasive cancer;<sup>12</sup> in this sample, 13.9% of women had HER2 positive. The mean Ki-67 of the present study was 34.1%. A standard cut-off point for the Ki-67 index has not been established due to the different methodologies used, ranging from 3.5 to 34%, but these cut-off points are inconclusive. Ki-67 is an important predictor of neoadjuvant or adjuvant treatment, and the higher its index (%), the greater the cell proliferation and lower the survival. The literature reveals that healthy breast cells have Ki-67 lower than 3%.<sup>15</sup>

Age at diagnosis is also an important prognostic factor. In this study, half of the sample consisted of older adults (>60 years)

**Table 1.** Clinical, demographic, and anthropometric characteristics of women with invasive breast cancer.

Variable	n	%
Age		
≤39	12	7.2
40–49	28	16.9
50–59	43	25.9
60–69	51	30.7
≥70	32	19.3
Neoadjuvant chemotherapy		
Yes	74	44.5
No	92	55.5
Hypertension		
Yes	90	54.2
No	76	45.8
Diabetes Mellitus		
Yes	27	16.3
No	139	83.7
BMI classification		
Underweight	14	8.4
Normal	49	29.5
Overweight	38	22.9
Obesity	65	39.2
Blood glucose level		
Up to 99 mg/dL	63	38.2
100–125 mg/dL	81	49.1
≥126 mg/dL	21	12.7

BMI: body mass index.

and 24% were up to 50 years of age, similarly to literature data, which show that approximately 50% of breast cancer cases occur in 65-year-old women or older,<sup>22</sup> and 20% in women younger than 50 years of age.<sup>12</sup>

In the present study, according to BMI, over half of the sample (62.1%) had excess weight (39.2% overweight and 22.9% obesity). Hankó-Bauer et al. found this same scenario when they analyzed obesity in women with breast cancer, revealing that 62.45% of the sample were overweight and obese (33.07 and 29.38%, respectively).<sup>10</sup>

The number of cases of overweight and obesity is increasing around the world. In Brazil, 50.5% of women are overweight,<sup>23</sup> which suggests that it is common for women with breast cancer also to be overweight. Obesity is associated with both an increased risk of developing breast cancer and worse prognosis of the disease, but their relationship is also complex.<sup>12</sup> Studies

**Table 2.** Distribution of invasive breast cancer patients according to tumor characteristics.

Variable	n	%
Tumor size		
T1 (≤2cm)	65	39.2
T2 (2–5 cm)	62	37.3
T3 (>5 cm)	16	9.6
T4 (*)	23	13.9
Lymph node involvement		
N0	87	52.4
N1	51	30.7
N2	24	14.5
N3	04	2.4
Metastasis		
Yes	01	0.6
No	165	99.4
Grade		
G1	23	13.8
G2	75	45.2
G3	68	41
Estrogen receptor		
Positive	134	80.7
Negative	32	19.3
Progesterone receptor		
Positive	123	74
Negative	43	26
HER2		
Positive	23	13.9
Negative	143	86.1

\*Tumor of any size with skin or chest wall invasion.

show that the main hypothesis is that excess fat tissue promotes a hormonal imbalance, and increases insulin and circulating insulin-like growth factor (IGF-1); and that adipocytes producing pro-inflammatory factors, such as tumor necrosis factor (TNF), interleukin, and C-reactive protein, induces the progression of the cell cycle and apoptosis inhibition, raising the risk

of developing cancer. In addition, the factors mentioned might promote overexpression of oncogenes,<sup>24</sup> oxidative stress, and changes in immune function.<sup>3</sup>

In the current study, we analyzed the relationship between nutritional status and prognostic factors and found no significant association between BMI and tumor size, lymph node

**Table 3.** Association of fasting blood glucose and body mass index (BMI) with prognostic factors in women with invasive breast cancer.

Variable	BMI			Fasting Blood Glucose		
	N	Mean±SD	p-value	N	Mean±SD	p-value
Age (years)						
≤39	12	26.89±4.07	0.58	12	97.25±8.04	0.01
40–49	28	29.30±6.50		28	109.21±33.31	
50–59	43	29.40±5.93		43	106.65±21.01	
60–69	51	29.22±5.80		51	112.57±20.96	
≤70	32	28.12±5.91		32	113.25±24.43	
Tumor size						
T1	65	28.38±6.12	0.63	65	110.25±24.54	0.78
T2	62	29.34±5.73		62	108.06±17.81	
T3	16	27.90±4.88		16	102.50±9.79	
T4	23	29.86±6.12		23	116.09±37.83	
Lymph node involvement						
N0	87	29.17±5.67	0.43	87	107.36±20.34	0.03
N1	51	28.16±6.15		51	107.02±20.02	
N2	24	29.29±6.33		24	118.21±35.52	
N3	4	30.19±2.82		4	135.25±31.05	
Metastasis						
No	165	28.90±5.87	0.94	165	109.56±23.77	0.72
Yes	1	29.31		1	99.00	
Grade						
G1	23	29.06±5.23	0.79	23	106.61±18.39	0.36
G2	75	29.12±5.80		75	112.84±28.64	
G3	68	28.60±6.17		68	106.78±18.55	
Menopausal status						
Pre	32	28.45±6.40	0.58	32	103.00±18.57	0.02
Post	134	29.01±5.73		134	111.04±24.58	
Progesterone receptor						
Positive	123	29.36±5.89	0.11	123	111.64±24.96	0.01
Negative	43	27.59±5.61		43	103.35±18.60	
Estrogen receptor						
Positive	134	29.09±5.89	0.52	134	110.89±24.20	0.03
Negative	32	28.09±5.69		32	103.66±20.88	
HER2						
Negative	143	28.86±5.84	0.65	143	110.44±24.94	0.4
Positive	23	29.16±6.06		23	103.61±12.61	

SD: standard deviation.

involvement, metastasis, histological grade, hormone receptors, HER2, and Ki-67. These results differ from those of other studies that, after associating obesity with prognostic factors, revealed that overweight women with breast cancer had larger tumors and lymph node involvement.<sup>10,25,26</sup> Daling et al., while studying the relationship between BMI and tumor markers in 1,177 North-American women with invasive breast cancer, found that those who were in the highest BMI quartile had larger tumors, higher histological grade, estrogen receptor negative, and more significant expression of Ki-67, when compared to women with tumor who were in the first BMI quartile.<sup>27</sup>

Currently, there are several anthropometric measures to assess excess fat in individuals. Among them, BMI is the most widely used method to classify overweight or obesity in adult populations for being simple, fast, and easy to apply and measure. However, when compared to methods that assess body composition, BMI shows an imprecise estimate of fat and lean mass. Some authors have questioned its use in diagnosing body fat.<sup>28</sup>

In this study, we did not adopt other anthropometric variables to analyze body fat distribution, such as waist circumference (WC) and waist-hip ratio (WHR). A Brazilian study by Felden and Figueiredo investigated the relationship between body fat distribution and breast cancer patients and revealed that women with WC > 88 cm were 2.08 times more likely to develop the disease than those with normal measures, not finding an association of BMI and WHR with breast cancer.<sup>29</sup> A research conducted in the same institution with 2040 women with breast cancer, who had a profile similar to the participants in the current study, indicated that patients with greater abdominal fat (WC and WHR) had larger tumors and lymph node involvement; and, after analyzing the BMI and prognostic factors, it found no significant difference.<sup>30</sup> These findings could suggest that abdominal obesity is more significant when analyzing the relationship between overweight and prognostic factors in breast cancer than assessing overall obesity.

Regarding comorbidities, more than half of the sample (54.2%) had SAH. According to the Ministry of Health, 25.7%

of the population has this pathology. The relationship between hypertension and breast cancer is still inconsistent in the literature. A study revealed that hypertension before a breast cancer diagnosis was associated with worse survival, particularly for African-American women.<sup>31</sup> The results of studies with animal models and humans suggest that hypertension can increase the carcinogenic response and initiate the carcinogenesis process. However, further studies are necessary to understand this association.<sup>32</sup>

Among the women participating in this research, 16.3% had diabetes mellitus, corroborating a study conducted in Mexico with a sample of 265 invasive breast cancer patients, in which 15% were diabetic.<sup>16</sup> In the present study, despite the low percentage of diabetic patients, over half of the sample (62%) presented pre-surgical hyperglycemia (blood glucose level >99 mg/dL). Among non-diabetic patients, 51.8% had blood glucose level between 100 and 125 mg/dL, belonging to the category of increased risk for the development of this comorbidity, and 4.3% had blood glucose level  $\geq$ 126 mg/dL, classified in the indicator of diabetes mellitus category, according to the American Diabetes Association.<sup>18</sup> A recent study with women with breast cancer found higher blood glucose and insulin levels in non-diabetic patients.<sup>33</sup>

The present study showed a significant association between hyperglycemia and more advanced age, higher lymph node involvement, hormone receptor positive, and post-menopausal status. These results are in line with a similar study, conducted in the same institution, which revealed that women with fasting blood glucose above 100 mg/dL in the preoperative period had

**Table 5.** Association between fasting blood glucose and body mass index (BMI) of women with invasive breast cancer.

Fasting blood glucose	BMI (Mean $\pm$ SD)	p-value
$\leq$ 99 mg/dL	27.6 $\pm$ 5.04	0.03
100–125 mg/dL	29.9 $\pm$ 5.09	
$\geq$ 126 mg/dL	28.6 $\pm$ 7.13	

SD: standard deviation.

**Table 4.** Association between body mass index (BMI) and comorbidities of women with invasive breast cancer.

Variable	BMI				p-value
	Underweight (%)	Normal (%)	Overweight (%)	Obesity (%)	
Hypertension					
No (n=76)	10.5	31.6	32.9	25.0	0.03
Yes (n=90)	6.7	27.8	14.4	51.1	
Diabetes Mellitus					
No (n=76)	7.9	28.8	23.7	39.6	0.86
Yes (n=90)	11.1	33.3	18.5	37.0	

larger tumors and lower survival.<sup>30</sup> Villarreal-Garza identified decreased survival in patients with hyperglycemia — diabetic or not —, and a higher risk of death for women with serum glucose levels greater than 130 mg/dL.<sup>16</sup> Studies indicate an association of hyperglycemia with a worse prognosis of breast cancer and larger tumors.<sup>16,17</sup> According to Erickson et al., hyperglycemia can directly influence the progress and outcomes of breast cancer through several mechanisms, including high levels of insulin and insulin-like growth factors, sex hormones, and inflammatory markers.<sup>17</sup>

Similarly to our results, a study performed with women with breast cancer in Southern Brazil did not identify a significant

association of menopausal status with tumor characteristics and anthropometric variables.<sup>29</sup>

The current findings show that nutritional status, classified according to BMI, had no association with prognostic factors. These results might suggest the need for other complementary anthropometric methods, such as waist circumference and waist-hip ratio, for a better nutritional diagnosis. Nonetheless, patients with fasting hyperglycemia had a more advanced age, higher lymph node involvement, hormone receptor positive, and post-menopausal status. Considering that overweight and hyperglycemia are modifiable risk factors, we can adopt new practices to improve nutritional intervention.

## REFERENCES

1. Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de Prevenção e Vigilância. Estimativa 2018: Incidência de Câncer no Brasil. Rio de Janeiro: Instituto Nacional de Câncer José Alencar Gomes da Silva, Coordenação de Prevenção e Vigilância; 2017.
2. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series (894). Geneva: World Health Organization; 2000.
3. World Cancer Research Fund; American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, D.C.: American Institute for Cancer Research; 2007.
4. Rock C, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya K, Schwartz A, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62(4):243-74. <https://doi.org/10.3322/caac.21142>
5. Carmichael A. Obesity as a risk factor for development and poor prognosis of breast cancer. *Int J Obstetr Gynaecol*. 2006;113(10):1160-6. <https://doi.org/10.1111/j.1471-0528.2006.01021.x>
6. Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. Diretrizes brasileiras de obesidade. 4ª ed. São Paulo: Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica; 2016.
7. Kamineneni A, Anderson M, White E, Taplin S, Porter P, Ballard-Barbash R, et al. Body mass index, tumor characteristics, and prognosis following diagnosis of early-stage breast cancer in a mammographically screened population. *Cancer Causes Control*. 2013;24(2):305-12. <https://doi.org/10.1007/s10552-012-0115-7>
8. Diana C, Diana E, Alzamora N, Vilanova A, Climent J, Albaladejo C. Factores pronósticos del cáncer de mama. Modelo predictivo. *Rev Oncol*. 2004;6(8):472-82. <https://doi.org/10.1007/BF02713084>
9. Batschauer A. Avaliação hemostática e molecular em mulheres com câncer de mama receptor hormonal negativo [dissertação]. Belo Horizonte: Faculdade de FARMÁCIA, Universidade Federal de Minas Gerais; 2009.
10. Hankó-Bauer O, Georgescu R, Coros M, Boros M, Barsan I, Stolnicu S. Correlation between obesity and prognostic/predictive parameters with emphasis on the importance of lymph node metastases in patients with invasive breast carcinoma. *Pol J Pathol*. 2017;68(1):33-9. <https://doi.org/10.5114/pjp.2017.67613>
11. Makki J. Diversity of Breast Carcinoma: Histological Subtypes and Clinical Relevance. *Clin Med Insights: Pathol*. 2015;8:23-31. <https://dx.doi.org/10.4137%2FCPath.S31563>
12. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin J, Friedman E, Slingerland J. Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. *CA: Cancer J Clin*. 2017;67(5):378-97. <https://doi.org/10.3322/caac.21405>
13. Abreu E, Koifman S. Fatores Prognóstico no câncer de mama feminina. *Rev Bras Cancerol*. 2002;48(1):113-31.
14. Buitrago F, Uemura G, Sena MCF. Fatores prognósticos em câncer de mama. *Com Ciências Saúde*. 2011;22(Sup. 1):S69-82.
15. Pathmanathan N, Balleine R. Ki67 and proliferation in breast cancer. *J Clin Pathol*. 2013;66(6):512-6. <https://doi.org/10.1136/jclinpath-2012-201085>
16. Villarreal-Garza C, Shaw-Dulin R, Lara-Medina F, Bacon L, Rivera D, Urzua L, et al. Impact of Diabetes and Hyperglycemia on Survival in Advanced Breast Cancer Patients. *Experim Diabetes Res*. 2012;2012:1-8. <http://dx.doi.org/10.1155/2012/732027>
17. Erickson K, Patterson R, Flatt S, Natarajan L, Parker B, Heath D, et al. Clinically Defined Type 2 Diabetes Mellitus and Prognosis in Early-Stage Breast Cancer. *J Clin Oncol*. 2011;29(1):54-60. <https://doi.org/10.1200/JCO.2010.29.3183>
18. Instituto Nacional de Câncer José de Alencar Gomes da Silva. TNM: classificação de tumores malignos. 6ª ed. Rio de Janeiro: Instituto Nacional de Câncer José de Alencar Gomes da Silva; 2004. 254p.
19. Organização Pan-Americana de Saúde. Informe preliminar da 36ª Reunión del Comité Asesor de Investigaciones en Salud: Encuesta Multicéntrica – Salud Bienestar y Envejecimiento (SABE) en América Latina y el Caribe. Organización Pan-Americana de Saúde; 2002.



20. American Diabetes Association. Standard of Medical Care in Diabetes – 2017. *Diabetes Care*. 2017;40 (Supl. 1).
21. Anderson W, Chatterjee N, Ershler W, Brawley O. Estrogen Receptor Breast Cancer Phenotypes in the Surveillance, Epidemiology, and End Results Database. *Breast Cancer Res Treat*. 2002;76(1):27-36.
22. Gennari R, Curigliano G, Rotmensz N, Robertson C, Colleoni M, Zurrada S, et al. Breast carcinoma in elderly women. *Cancer*. 2004;101(6):1302-10. <https://doi.org/10.1002/cncr.20535>
23. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância de Doenças e Agravos não Transmissíveis e Promoção da Saúde. *Vigitel Brasil 2016: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados brasileiros e no Distrito Federal em 2016*. Brasília: Ministério da Saúde; 2017.
24. Barros A, Barros M. HER e câncer de mama: inter-relações biológicas, prognósticas e terapêuticas. São Paulo: Roche; 2006.
25. Loi S, Milne R, Friedlander M, McCredie M, Giles G, Hopper J, et al. Obesity and Outcomes in Premenopausal and Postmenopausal Breast Cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14(7):1686-91. <https://doi.org/10.1158/1055-9965.EPI-05-0042>
26. Rosenberg L, Czene K, Hall P. Obesity and poor breast cancer prognosis: an illusion because of hormone replacement therapy? *Brit J Cancer*. 2009;100(9):1486-91. <https://dx.doi.org/10.1038/2Fsj.bjc.6605025>
27. Daling J, Malone K, Doody D, Johnson L, Gralow J, Porter P. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. *Cancer*. 2001;92(4):720-9.
28. Nunes R, Clemente E, Pandini J, Cobas R, Dias V, Sperandei S, et al. Confiabilidade da classificação do estado nutricional obtida através do IMC e três diferentes métodos de percentual de gordura corporal em pacientes com diabetes melito tipo 1. *Arq Bras Endocrinol Metab*. 2009;53(3):360-7. <http://dx.doi.org/10.1590/S0004-27302009000300011>
29. Felden J, Figueiredo A. Distribuição da gordura corporal e câncer de mama: um estudo de caso-controle no Sul do Brasil. *Ciência Saúde Coletiva*. 2011;16(5):2425-33. <http://dx.doi.org/10.1590/S1413-81232011000500011>
30. Gioseffi C. Relação da adiposidade central e glicemia de jejum com características tumorais e sobrevida global em mulheres com câncer de mama [dissertação]. Rio de Janeiro: Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro; 2017.
31. Tammemagi C, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and Survival Disparities Among Black and White Patients With Breast Cancer. *JAMA*. 2005;294(14):1765-72. <https://doi.org/10.1001/jama.294.14.1765>
32. Zhu Q, Xu W, Tao M. Biomarkers of the Metabolic Syndrome and Breast Cancer Prognosis. *Cancers*. 2010;2(2):721-39. <https://dx.doi.org/10.3390/2Fcancers2020721>
33. Ferroni P, Riondino S, Laudisi A, Portarena I, Formica V, Alessandroni J, et al. Pretreatment insulin levels as a prognostic factor for breast cancer progression. *Oncologist*. 2016;21:1041-9. <https://doi.org/10.1634/theoncologist.2015-0462>

# USE OF DERMOGLANDULAR FLAP (BUROW'S TRIANGLE) AFTER NEOADJUVANCE IN UPPER QUADRANT TUMORS OF THE BREAST

Uso de retalho dermoglandular (triângulo de Burow) pós neoadjuvância em tumores do quadrante superior da mama

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## ABSTRACT

Mastectomy has been, in the past, the first treatment of choice for locally advanced breast tumors, especially when the neoadjuvant response is partial, and the tumor's location doesn't allow an aesthetic outcome when using usual quadrantectomy. Oncoplastic techniques are good solutions for these tumors allowing to resect big areas, removing the whole tumor and preserving breast symmetry. This case describes a dermoglandular flap technique to be used in advanced upper quadrant tumors in post neoadjuvance patients.

**KEYWORDS:** Breast reconstruction; Mammoplasty; Neoadjuvant therapy; Breast cancer; Surgical flap.

## RESUMO

A mastectomia foi, no passado, o tratamento de escolha para tumores localmente avançados da mama, especialmente quando a resposta neoadjuvante é parcial e a localização tumoral não permite um bom resultado estético usando como técnica a quadrantectomia. Técnicas oncoplásticas são ótimas opções para esses tumores, uma vez que se ressecam grandes áreas, removendo todo o tumor e preservando a simetria mamária. Este caso descreve uma técnica de retalho dermoglandular a ser usado em tumores do quadrante superior em uma paciente pós-neoadjuvância.

**PALAVRAS-CHAVE:** reconstrução da mama; mamoplastia; terapia neoadjuvante; câncer de mama; retalhos cirúrgicos.

Study carried out at Hospital Universitário Antônio Pedro – Niterói (RJ), Brazil.

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## INTRODUCTION

Neoadjuvant systemic treatment has been the choice for locally advanced tumors as an attempt to improve surgical options and decrease the necessity of mastectomies without reducing the oncological benefit<sup>1</sup>.

The reconstruction of partial defects of the breast in the upper quadrants took Grisotti and Calabrese to describe the area as a "no man's land". The use of dermoglandular flaps is a good oncoplastic choice to maintain breast symmetry without the need to operate the opposite breast. The Burow's triangle flap is indicated for tumors of upper medial quadrants and union of upper quadrants<sup>2</sup>.

This case report shows the combination of oncoplastic techniques in a locally advanced tumor after neoadjuvant therapy and whose response was not satisfactory to obtain oncological and esthetics benefits.

## CASE REPORT

R.B.M., 35 years old, black, without comorbidities, came to the mastology service of Antonio Pedro University Hospital in August 2016 with a five-centimeter tumor in the union of upper quadrants of the right breast, with an evolution of one year and core biopsy showing a ductal invasive carcinoma (T2N0M0). The patient was referred to a neoadjuvant systemic treatment, where she had six sessions of FAC (Fluorouracil, Adriamycin and Cyclophosphamide) with partial pathological response.

In February 2017, there was still some palpable mass, very close to the skin, of about 2-3 centimeters. She was, then, submitted to a breast conservation surgery with resection of the tumor and the skin above, complemented by a dermoglandular rotation flap, the Burow's triangle (Figures 1, 2 and 3). The tissue removed showed a 2,5x2,5x2,5-cm tumor with free margins and eight negative lymph nodes.

## DISCUSSION

The use of primary systemic treatment or neoadjuvant systemic treatment (NST) has been accepted as the treatment of choice for patients with locally advanced disease. It is usually used in breast cancer patients with three purposes: to improve surgical options (several randomized trials have shown tumor's down-stage and decreased number of mastectomies), to obtain information on response (early response after two or three cycles of chemotherapy has been shown to be a predictor of pathological complete remission and might, therefore, serve as a predictor of long-term outcome) and to obtain long-term disease-free survival (absence of all viable tumor tissue is considered to predict the complete eradication of distant micro metastatic residual diseases)<sup>2</sup>.

Several studies in early tumors, has showed no significant difference in survival when conservative surgery is chosen over a radical approach. Van Dongen et al. showed no difference in 10-year follow ups of tumors of up to five centimeters in overall survivor and distant metastasis free-survival<sup>3</sup>. Locally advanced tumors are still a controversial subject. Larger tumors require larger resections which can affect breast symmetry and often leads to a mastectomy, especially when the tumor is located in the upper quadrants, where defects are more difficult to repair.

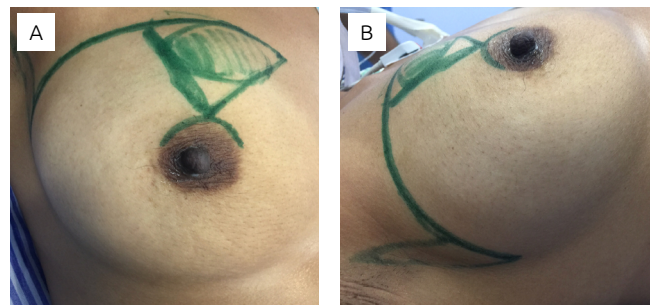


Figure 1. Breast tumor and Burow's triangle draw.

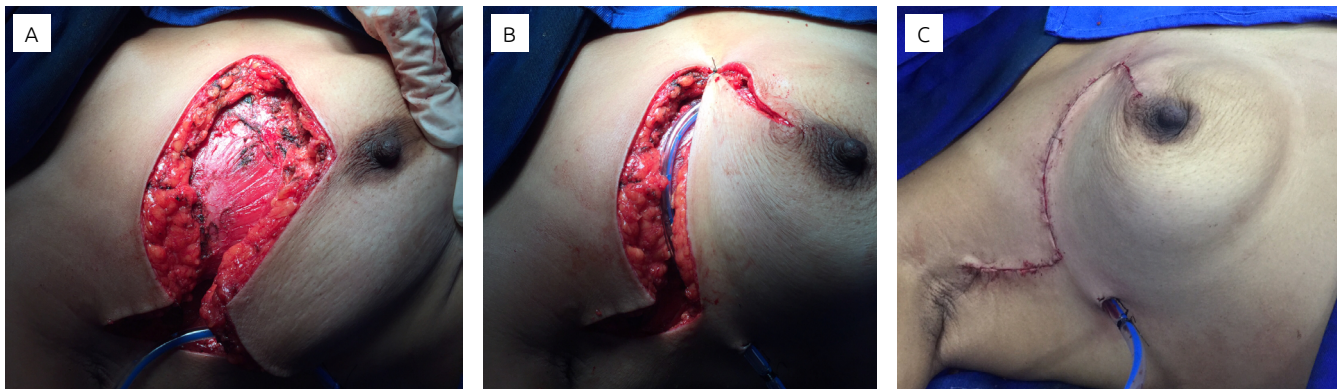


Figure 2. Sequence: defect after tumor and skin resection; replacement of the tissue and closure; defect closed after tissue displacement.

Oncoplastic techniques have been growing bigger in mastology the past few years and shown as an alternative to mastectomies in larger tumors. It applies reconstructive techniques for wider excisions to remodel the breast and maintain its symmetry<sup>4</sup>. It allows wider resections with wider negative margins and better aesthetic satisfaction<sup>5</sup>.

Rietjens showed that there was no difference in the disease's outcomes when using oncoplastic techniques after 74 months of follow-up<sup>6</sup>. Also, other papers demonstrated no difference in overall survivor, loco-regional recurrence and quality of life using oncoplastic techniques and reinforced the fact that it is possible to take away more tissue than usual without losing breast symmetry<sup>7</sup>.

Broecker and Regano used patients submitted to neoadjuvant therapies and oncoplastic techniques and compared prognostic factors. In both cases, there was more indication of conservative surgery with no increase in positive margins, re-excisions and ipsilateral recurrence. Regano et al.<sup>8</sup> displayed better aesthetics satisfaction and Broecker et al. showed no difference between disease specific survival and completion mastectomy rate in five years<sup>9</sup>. These studies demonstrate oncoplastic surgery safety after neoadjuvant therapy.

Breast cancer treatment requires a multidisciplinary approach and evaluation of patients' expectancies. An immediate reconstruction allows for anatomy maintenance, preserving the inframammary fold and more of the breast's native tissue<sup>10</sup>.

Immediate reconstructions using tissues rearrangements have less complications and better aesthetic results than those using larger flaps such as the dorsal one<sup>11</sup>.

The Burow's operation was first described in the early nineteenth century to facilitate the movement of flaps. The Burow's wedge/triangle flap is a surgical maneuver used to close triangular defects<sup>12</sup>. It has been widely used to close facial defects. The tumor is resected from a primary triangle and the tissues from the areas beyond the sides of the wound are mobilized to close the primary defect.

When used to repair upper breast tumor resection defects, the tissue displacement area provides good axillary approach with no need for a secondary incision.

Although the use of Burow's technique is great to correct upper tumor defects after resections of the tumor and the skin above, it can displace the nipple and areola. Thus, using this technique assumes comparison with the contralateral breast and, if necessary, repositioning the areola about 1 centimeter in the opposite direction of the resection.

This technique has many variants and can be of great use in patients with upper quadrant tumors, who want to maintain the breast's aspect and symmetry and have no desire of operating the contralateral breast. The only negative point of this operation is the scar, which is large and can disturb some patients.

Oncoplastic techniques can greatly enhance the number of options in breast cancer surgery, avoiding the old quadrantectomy-mastectomy rule and offering patients new perspectives. The greatest reason for a patient to choose mastectomy without reconstruction is their fear of cancer recurrence. The best antidote to this fear is to offer good conservative options that are both safe and cosmetically sound<sup>13</sup>.

## CONCLUSION

Breast cancer therapy requires a multidisciplinary approach, especially when it comes to locally advanced tumors. Neoadjuvant systemic therapy has been shown as the treatment of choice for these patients, once that it helps to predict a tumor's prognosis and allows better surgical options once the tumor is downstaged.

Surgical options, once we use oncoplastic techniques, are safer and more aesthetic, since they allow greater tissue removal and better margins while maintaining breast symmetry<sup>14</sup>.

In this scenario, we can reduce mastectomy rates in locally advanced tumors, offering patients better results without jeopardizing oncological safety. In order to do so, training in oncoplastic surgery is necessary, so that better surgical techniques can be applied and aesthetic results can be maintained without reducing quality of life and local control, optimizing operative time, and reducing adverse effects and costs<sup>15</sup>.



**Figure 3.** Sequency: first day after the procedure; one month after the procedure; six months after the procedure.

## REFERENCES

1. Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. *J Clin Oncol*. 2006;24:1940-9.
2. Lucena CEM, Paulinelli RR, Pedrini JL. *Oncoplastia e reconstrução mamária*. Rio de Janeiro: Medbook; 2017.
3. van Dongen JA, Bartelink H, Fentiman IS, Lerut T, Mignolet F, Olthuis G, et al. Factors influencing local relapse and survival and results of salvage treatment after breast-conserving therapy in operable breast cancer: EORTC trial 10801, breast conservation compared with mastectomy in TNM stage I and II breast cancer. *Eur J Cancer*. 1992;28(4-5):801-5. [https://doi.org/10.1016/0959-8049\(92\)90118-L](https://doi.org/10.1016/0959-8049(92)90118-L)
4. Clough KB, Kaufman GJ, Nos C, Buccimazza I, Sarfati IM. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. *Ann Surg Oncol*. 2010;17:1375-91. <https://doi.org/10.1245/s10434-009-0792-y>
5. Losken A, Dugal CS, Styblo TM, Carlson GW. A meta-analysis comparing breast conservation therapy alone to the oncoplastic technique. *Ann Plast Surg*. 2014;72(2):145-9. <https://doi.org/10.1097/SAP.0b013e3182605598>
6. Rietjens M, Urban CA, Rey PC, Mazzarol G, Maisonneuve P, Garusi C, et al. Long-term oncologic results of breast conservation treatment with oncoplastic surgery. *Breast*. 2007;16(4):387-95. <https://doi.org/10.1016/j.breast.2007.01.008>
7. Bogusevicius A, Cepulienė D, Sepetauskiene E. The integrated evaluation of the results of oncoplastic surgery for locally advanced breast cancer. *Breast J*. 2014;20:53-60. DOI: 10.1111/tbj.12222
8. Regano S, Hernanz F, Ortega E, Redondo-Figuero C, Gómez-Fleitas M. Oncoplastic techniques extend breast-conserving surgery to patients with neoadjuvant chemotherapy response unfit for conventional techniques. *World J Surg*. 2009;33:2082-6. <https://doi.org/10.1007/s00268-009-0152-x>
9. Broecker JS, Hart AM, Styblo TM, Losken A. Neoadjuvant therapy combined with oncoplastic reduction for high-stage breast cancer patients. *Ann Plast Surg*. 2017 Jun;78(6S Suppl 5):S258-62. <https://doi.org/10.1097/SAP.0000000000001062>
10. Cordeiro PG. Breast reconstruction after surgery for breast cancer. *N Engl J Med*. 2008;359:1590-601. <https://doi.org/10.1056/NEJMct0802899>
11. Kronowitz SJ, Feledy JA, Hunt KK, Kuerer HM, Youssef A, Koutz CA, et al. Determining the optimal approach to breast reconstruction after partial mastectomy. *Plast Reconstr Surg*. 2006;117:1-11; discussion 12-4.
12. Gormley DE. A brief analysis of the Burow's wedge/triangle principle. *J Dermatol Surg Oncol*. 1985;11(2):121-3.
13. Nold RJ, Beamer RL, Helmer SD, McBoyle MF. Factors influencing a woman's choice to undergo breast-conserving surgery versus modified radical mastectomy. *Am J Surg*. 2000;180:413-8.
14. Figueiredo CL, Pires DM, Mendonça ACG, Valadares CN, Andrade RL, Urban CA. Locoregional Flaps in Oncoplastic Surgery and Breast Reconstruction. *Mastology*. 2017;27(2):135-43. DOI: 10.5327/Z2594539420170000184
15. Pires DM, Gazoto Junior O, Valadares CN, Andrade RL. Training in oncoplastic and reconstructive breast surgery: analysis of training in America and in the European Union with the Brazilian reality. *Mastology*. 2017;27(2):164-71. DOI: 10.5327/Z2594539420170000185

# SURGICAL CORRECTION OF POLYMASTIA AND POLYTELIA WITH AN UNCOMMON PRESENTATION

## Correção cirúrgica de polimastia e politelia com apresentação incomum

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### ABSTRACT

Polymastia is a rare condition that is present in 1 to 5% of the population. Clinically, it is characterized by the presence of two or more breasts, which can occur in males or females. The condition may appear with or without the presence of extra nipples, which is termed polythelia. Bilateral presentation is uncommon. Here we report a case of a patient who had more than one pair of breasts and extra nipples which were surgically corrected.

**KEYWORDS:** Breast; breast diseases; mammoplasty.

### RESUMO

Polimastia é uma condição rara presente em 1 a 5% da população. Clinicamente se caracteriza pela presença de duas ou mais mamas e pode ocorrer em homens ou mulheres. Essa condição pode se apresentar com ou sem a presença de mamilos extras, ou seja, politelia. A apresentação bilateral é incomum. Aqui apresentamos um caso de uma paciente que tinha mais de um par de mamas e mamilos extras que foram removidos cirurgicamente.

**PALAVRAS-CHAVE:** Mama; doenças mamárias; mamoplastia.

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## INTRODUCTION

Polymastia is a term used to describe the presence of more than two breasts in humans<sup>1</sup> and is synonymous with accessory or supernumerary breast tissue. This condition occurs when a failure occurs in the embryonic development of breast tissue. It is usually an asymptomatic condition but can cause anxiety, cosmetic problems, pain or restriction of movement<sup>2</sup>.

Its incidence varies around 1-5% of the population, with the armpit being the most frequent site of onset<sup>3</sup>. It can be identified during or before puberty and during pregnancy. Usually, the accessory breast tissue appears sporadically, but it is also suspected that it may be a hereditary condition, once that the abnormality is often found among relatives<sup>4</sup>. Bilateral presentation is infrequent and no reports similar to the one described have been found in the literature, in which the patient presents more than one pair of extra breasts and nipples.

## CASE REPORT

A 12-year-old female patient was referred to the mastology clinic for the presence of multiple nipples. Physical examination revealed the presence of extra breast in the bilateral axillary region of two pairs of areola papillary complexes (APC) on the breasts and two additional pairs of APCs (Figure 1), located bilaterally in the axilla and in the abdominal region. One of the paired mammary papillae does not have an areola.

It was decided to perform surgical correction, with excision of the accessory breast tissue and extra APCs (Figure 2). Removal of the breast tissue was performed through spindle

incisions, followed by subcutaneous approach and closure of the skin with intradermal suture with 4-0 monocryl wire. There were left two penrose drains, removed the next day. The histopathologic revealed to be a breast tissue with no signs of malignancy. The patient returned four months later for a follow-up and was asymptomatic and satisfied with the results (Figure 3).



Figure 2. Preoperative marking.



Figure 1. Extra breast in bilateral axillary region, pair of supernumerary mammary papillae in the thorax and pair of supernumerary mammary papillae in the abdomen.

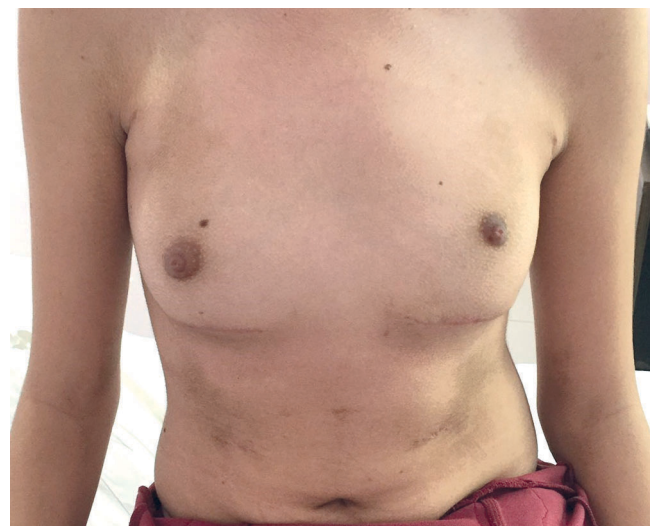


Figure 3. Final result four months after surgery.

## DISCUSSION

During the sixth week of embryonic development, the mammary line, which represents two ectodermal thickenings, develops along the sides of the embryo, extending from the axillary region to the groin. In normal development, most of the embryonic mammary peaks disappear, except for the two segments in the pectoral region, which later become breasts. Regression failure in any portion of the mammary ridge can lead to polymastia, with or without an APC. Therefore, the ectopic breast usually occurs along the “milk line” or breast line<sup>5</sup>.

Ectopic mammary tissue can also be located on the face<sup>6</sup>, the foot<sup>7</sup>, the back<sup>8</sup>, the perineum<sup>9</sup>, and the anus<sup>10</sup>. These locations outside the mammary line can be explained by the migration of primordial mammary cells during the development of the chest wall or through the modification of apocrine sweat glands<sup>4</sup>.

The accessory mammary tissue has the same capacity to undergo benign and malignant alterations as the normal mammary tissue<sup>11</sup>; however, the incidence of carcinoma in the accessory breast tissue is rare, corresponding to only 0.3% of the breast carcinomas<sup>12</sup>. There are multiple reports of benign alterations, such as fibroadenomas<sup>4,13-15</sup> or hyperplasias<sup>16,17</sup>, but the incidence of these alterations in supernumerary breasts is uncertain. Polymastia may present in an aberrant form that is not accompanied by a nipple or areola and is commonly mistaken for lipoma, lymphadenopathy, or hidradenitis<sup>11</sup>.

Polytelia is the term used to designate the presence of accessory papillae, considered a benign congenital anomaly. They may bother the patient because of cosmetic concerns, pain and swelling during menstruation or milk secretion<sup>18</sup>. Polytelia has been associated with urinary abnormalities — such as supernumerary kidneys, renal insufficiency and renal carcinomas — which can be explained, in part, by the parallel embryological development of mammary structures and the genitourinary system<sup>5</sup>. In the present case, the patient had three pairs of extra nipples and no urinary malformations were identified.

Polytelia is more common in males than in females and more incident in the afrodescendant population than in the Caucasian<sup>19</sup>. Their incidence in the population varies between 0.22–5.60%, depending on factors such as genetic inheritance

and ethnicity<sup>20</sup>. Because supernumerary papillae are often clinically obvious, occasionally, when only a papilla or areola and papillae are present, biopsy is needed to establish a diagnosis. Supernumerary papillae may also be clinically confused with fibroids, lipomas, warts and nevi<sup>21</sup>.

The oldest and most commonly used classification was described by Kajava in 1915, who classified supernumerary mammary tissue into eight categories:

1. complete supernumerary breast, with papilla, areola and glandular tissue;
2. supernumerary breast without a areola, but with papilla and glandular tissue;
3. supernumerary breast without papilla, but with areola and glandular tissue;
4. only aberrant glandular tissue, without papilla and areola;
5. only papilla and areola, with glandular tissue replaced by fat (pseudomama);
6. only papilla (polytelia);
7. only areola (areolar polytelia);
8. presence of only a tuft of hairs (polytelia pilosa)<sup>22</sup>.

Accessory breast tissue is present from birth, but is often only diagnosed after puberty, pregnancy or lactation, a period in which symptoms become more evident, such as swelling and pain during menstruation and elimination of secretions during lactation. Still, many cases are asymptomatic. In cases of doubt, definitive diagnosis should be made through fine needle aspiration or excisional biopsy, as it may be confused with abscess or another cause<sup>23</sup>.

After being diagnosed, the recommended treatment is the surgical one, so that a simple excision of the tissue or a liposuction can be performed. Preoperative examinations should include ultrasonography to exclude the possibility of benign or malignant lesions. It is also recommended that patients with a family history of breast cancer undergo a radical resection instead of liposuction<sup>2</sup>. In the present case, it was decided to perform the removal of the breast tissue through spindle incisions, followed by subcutaneous approach and closure of the skin with intradermal suture. The patient is satisfied with the results four months after the operation.

## REFERENCES

1. Santos Junior LA, Eulálio Filho WMN, Medeiros Neto AM. Polimastia e politelia: imagem. *Rev Bras Mastologia*. 2016;26:24-5. <https://doi.org/10.5327/Z201600010006RBM>
2. Qian JG, Wang XJ, Yu AR, Zhou FH. Surgical correction of axillary accessory breast tissue: 12 cases with emphasis on treatment option. *J Plast Reconstr Aesthet Surg*. 2008;61(8):968-70. <https://doi.org/10.1016/j.bjps.2008.03.001>
3. Lourenço C, Brandão M. Polimastia Axilar: Um Diagnóstico no Puerpério. *Acta Med Port*. 2014;27(2):274.
4. Azoz MEH, Abdalla EA, Elhassan MM. Fibroadenoma in ectopic breast tissue: a case report. *Sudan Med J*. 2014;50(2):112-5. <http://dx.doi.org/10.12816/0015583>
5. Shin SJ, Sheikh FS, Allenby PA, Rosen PP. Invasive secretory (juvenile) carcinoma arising in ectopic breast tissue of the axilla. *Arch Pathol Lab Med*. 2001;125:1372-4. [https://doi.org/10.1043/0003-9985\(2001\)125%3C1372:ISJCAI%3E2.0.CO;2](https://doi.org/10.1043/0003-9985(2001)125%3C1372:ISJCAI%3E2.0.CO;2)
6. Koltuksuz U, Aydin E. Supernumerary breast tissue: a case of pseudomamma on the face. *J of Pediatr Surg*. 1997;32(9):1377-8.



7. Conde DM, Kashimoto E, Torresan RZ, Alvarenga M. Pseudomamma on the foot: an unusual presentation of supernumerary breast tissue. *Dermatology Online J*. 2006;12(4):7.
8. Shreshtha S. Supernumerary Breast on the Back: a Case Report: *Indian J Surg*. 2016;78(2):155-7. <https://dx.doi.org/10.1007%2Fs12262-016-1443-8>
9. Chung-Park M, Liu CZ, Giampoli EJ, Emery JD, Shalodi A. Mucinous adenocarcinoma of ectopic breast tissue of the vulva. *Arch Pathol Lab Med*. 2002;126(10):1216-8. [https://doi.org/10.1043/0003-9985\(2002\)126%3C1216:MAOEBT%3E2.0.CO;2](https://doi.org/10.1043/0003-9985(2002)126%3C1216:MAOEBT%3E2.0.CO;2)
10. Ho SP, Tseng HH, King TM, Chow PC. Anal phyllodes tumor in a male patient: a unique case presentation and literature review. *Diagn Pathol*. 2013;8:49. <https://doi.org/10.1186/1746-1596-8-49>
11. Burdick AE, Thomas KA, Welsh E, Powell J, Elgart GW. Axillary polymastia. *J Am Acad Dermatol*. 2003;49:1154-6. <https://doi.org/10.1016/S0190>
12. Rho JY, Juhng SK, Yoon KJ. Carcinoma originating from aberrant breast tissue of the right upper anterior chest wall: a case report. *J Korean Med Sci*. 2001;16(4):519-21. <https://doi.org/10.3346/jkms.2001.16.4.519>
13. Ayadi-Kaddour A, Khadhar A, Mlika M, Braham E, Ismail O, Zegal D, et al. Fibroadenoma in an ectopic vulvar breast gland: a common neoplasm in an uncommon site. *Pathologica*. 2014;106(1):32-4.
14. Mukhopadhyay M, Saha AK, Sarkar A. Fibroadenoma of the ectopic breast of the axilla. *Indian J Surg*. 2010;72:143-5. <https://doi.org/10.1007/s12262-010-0024-5>
15. Ortiz-Mendoza CM. Axillary ectopic breast tissue fibroadenoma: report of three cases and review of the literature. *Ginecol Obstet Mex*. 2012;80(2):99-103.
16. Shatzel J, Blum A, Khoury T, Milligan J, Skitzki JJ. Gynecomastia-like hyperplasia of axillary ectopic breast tissue in a young female. *Case Rep Pathol*. 2013;2013:634248. <http://dx.doi.org/10.1155/2013/634248>
17. Hayes MM, Konstantinova AM, Kacerovska D, Michal M, Kreuzberg B, Suvova B, et al. Bilateral Gigantomastia, Multiple Synchronous Nodular Pseudoangiomatous Stromal Hyperplasia Involving Breast and Bilateral Axillary Accessory Breast Tissue, and Perianal Mammary-Type Hamartoma of Anogenital Mammary-Like Glands: A Case Report. *Am J Dermatopathol*. 2016;38(5):374-83. <https://doi.org/10.1097/DAD.0000000000000498>
18. Grimshaw EC, Cohen PR. Supernumerary nipple and seminoma: case report and review of polythelia and genitourinary cancers. *Dermatol Online J*. 2013;19:4.
19. Kokavec R, Macúch J, Fedeles J, Ondriás F. Polythelia is not a mere aesthetic issue. *Acta Chirurgiae Plasticae*. 2002;44:3-6.
20. Galli-Tsinopoulou A, Krohn C, Schmidt H. Familial polythelia over three generations with polymastia in the youngest girl. *Eur J Pediatr*. 2001;160:375-7.
21. Cohen PR, Kurzrock R. Miscellaneous genodermatoses: Beckwith-Wiedemann syndrome, Birt-Hogg-Dube syndrome, familial atypical multiple mole melanoma syndrome, hereditary tylosis, incontinentia pigmenti, and supernumerary nipples. *Dermatol Clin*. 1995;13:211-29.
22. Leung AKC, Robson WLM. Polythelia. *Int J Dermatol*. 1989;28:429-33.
23. Farcy DA, Rabinowitz D, Frank M. Ectopic glandular breast tissue in a lactating young woman. *J Emerg Med*. 2011 Dec;41(6):627-9. <https://doi.org/10.1016/j.jemermed.2010.11.033>

# NECROTIZING FASCIITIS OF BREAST IN POSTPARTUM PERIOD: CASE REPORT

## Fasciíte necrotizante de mama no puerpério: relato de caso

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### ABSTRACT

Necrotizing fasciitis is an aggressive infection that affects subcutaneous and superficial fascia by necrosis, more often found in the abdominal wall, perineum and extremities. Rare cases have been described in the breast and the literature points to breastfeeding and previous breast procedures as risk factors for this condition. We present a 27-year-old patient in postpartum period who presented a right nipple fissure associated to breastfeeding, that evolved to a local aggressive infection with extensive necrosis of fascia and mammary parenchyma characterized as necrotizing fasciitis. Our aim is to highlight the importance of early diagnosis, especially to differentiate from puerperal mastitis which has a different pathophysiology and treatment, as well as the need for appropriate therapy consisting of surgical debridement and broad spectrum antibiotics in order to avoid further complications and death.

**KEYWORDS:** Necrotizing fasciitis; breast diseases; mastitis; lactation disorders.

### RESUMO

Fasciíte necrotizante é uma infecção agressiva que acomete o subcutâneo e fâscias superficiais por necrose, mais frequentemente encontrada em parede abdominal, períneo e extremidades. Raros casos foram descritos na mama e a literatura aponta a amamentação e procedimentos mamários prévios como fatores de riscos para essa condição. Apresentamos uma paciente no puerpério, de 27 anos, que apresentou uma fissura no mamilo direito associada à amamentação e que evoluiu com infecção local agressiva, com necrose extensa de fâscias e parênquima mamário caracterizada como fasciíte necrotizante. O trabalho visa apresentar a importância do diagnóstico precoce, principalmente com diferenciação para as mastites puerperais que possuem fisiopatologia e tratamento distintos, assim como a necessidade do tratamento adequado com desbridamento cirúrgico e antibioticoterapia de amplo espectro para evitar maiores complicações e o óbito.

**PALAVRAS-CHAVE:** Fasciíte necrosante; doenças mamárias; mastite; transtornos da lactação.

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## INTRODUCTION

Necrotizing fasciitis is an aggressive infection that affects the subcutaneous and superficial fascia by necrosis, and can be found more frequently in the abdominal wall, perineum and extremities<sup>1-3</sup>. Less than 20 cases were described in the breast and the literature points to breastfeeding and previous breast procedures as risk factors for this condition<sup>1</sup>. Therapeutic success depends on early diagnosis, institution of appropriate therapy and, especially, the differential diagnosis with puerperal abscesses secondary to lactational puerperal mastitis.

## CASE REPORT

A 27-year-old female patient with three pregnancies, two deliveries and one abortion at seven days postpartum had a right nipple fissure associated with breastfeeding, mastalgia, and hyperemia. She was treated for puerperal mastitis with cephalexin and ibuprofen. After three days, she sought medical help at the University Hospital of Brasília (HUB) for fever and intense mastalgia. She was tachycardic (105 bpm), with arterial blood pressure of 107 × 63 mmHg, axillary temperature of 36.6°C and SaO<sub>2</sub> 95% in ambient air. She presented right breast with hyperemia extending to the abdomen, dorsum and contralateral breast, as well as a violaceous lesion surrounding the nipple-areolar complex with central necrosis (Figures 1 and 2).

The patient was admitted and ceftriaxone with clindamycin were initiated. Mammary ultrasound did not show any fluid collections or abscess. Admission laboratory tests showed mild leukocytosis with no left deviation, CRP and HSV with a significant elevation, pro-calcitonin in the moderate sepsis risk range (0.698 ng/mL) without further alterations. Nursing controls at 12 hours revealed fever of 39.1°C, tachycardia (106

to 116 bpm) and blood pressure trend to hypotension. New laboratory tests on the subsequent day showed leukocytosis with left deviation and still very high CRP and HSV. The hospital's infection control unit suggested the use of sodium piperacillin with tazobactam sodium, vancomycin and clindamycin. Breast surgery department was called and, after discussion with all medical staffs, opted for immediate surgical debridement. The patient was referred to the operating room after adequate information in the presence of her relatives and a signed consent form. Initially, breast conserving surgery was attempted. However, once perceived intraoperatively that the necrotic area was too extensive, a mastectomy was the only choice with removal of some necrotic level 1 axillary lymph nodes, but not a complete axillary dissection. The specimen was sent to pathology and breast parenchyma fragments, far from the skin, were sent to microbiology. A 2-cm window on the chest wall suture was left open to monitor the vitality of the pectoralis major muscle. Breastfeeding was inhibited by cabergoline and contralateral breast wrapping. After one day at ward, the patient was sent to the Intensive Care Unit (ICU) due to dyspnea, desaturation in ambient air and hypotension. A chest angiotomography showed moderate bilateral pleural effusion, later attributed to rigorous venous hydration. Following improvement of symptoms in the sixth day of ICU care, she was sent to ward, and discharged the next day after completing the seven-day schedule of broad-spectrum venous antibiotic therapy. The window suture was closed 14 days after the mastectomy.

Blood culture was negative, but breast fragments came positive with *Streptococcus pyogenes* and *Staphylococcus warneri*. Pathology report revealed acute mastitis with extensive necrosis measuring 10.5 × 10.0 cm with abscessation of surrounding breast tissue (Figure 3), ulceration of the skin and overlying



**Figure 1.** Hyperemyroid, edemaciate right breast, with necrosis in the areola-papillary complex and a violaceous lesion surrounding its areola-papillary complex.



**Figure 2.** Hyperemia in the abdomen and dorsal region.

nipple, lactational lobular hyperplasia and absence of neoplasia in the sample.

## DISCUSSION

Necrotizing fasciitis is a rare aggressive infection (0.4 cases in 100,000 individuals)<sup>1</sup> with high mortality rates (between 25 and 73%)<sup>2</sup>. It affects the subcutaneous and superficial fascia by necrosis, and most frequently affects the abdominal wall, perineum and extremities<sup>2,3</sup>. It may be primary or idiopathic when there is no evident reason such as skin tear, or secondary when the source of infection is known. The secondary one is most frequent and can be precipitated by laceration, cut, abrasion, contusion, burn, bite, subcutaneous injection or surgical scar<sup>2</sup>. It is associated with immunodeficiency due to: alcoholism, chemotherapy, malignant neoplasms, use of corticoids, malnutrition, diabetes mellitus, polytrauma and peripartum period<sup>1-4</sup>.

According to microbial etiology, it can be divided into three types. Type I is polymicrobial, with at least one obligate anaerobic bacterium associated with one or more facultative anaerobes (non-A group *streptococci*) and enterobacteria. This type is associated with abdominal or perineal infections. Type II usually occurs in extremities, such as hemolytic streptococcal gangrene, and is caused by group A hemolytic *Streptococcus*. It may be associated with *Staphylococcus aureus*<sup>1</sup>, and *Streptococcus pyogenes* is the most common bacteria found in approximately one third of cases of necrotizing fasciitis<sup>3</sup>. Type III is associated

with wounds made by fish or in contact with sea water<sup>1</sup> caused by *Vibrio vulnificus*.

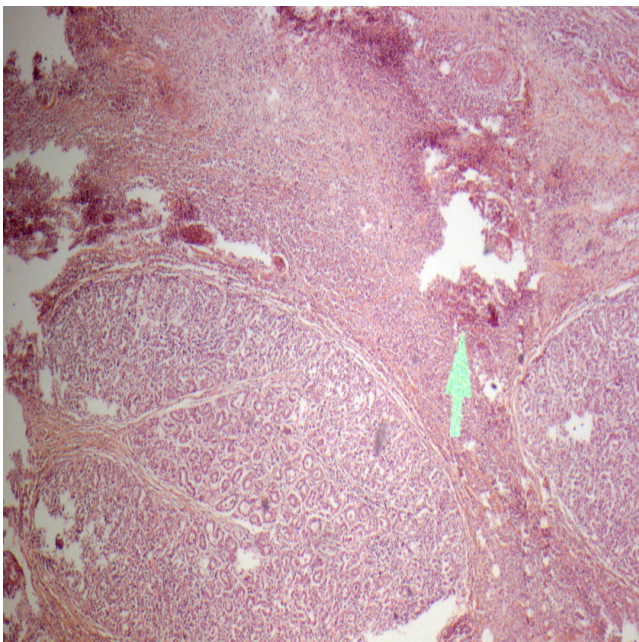
Mortality can be reduced by up to 10% with early diagnosis and intensive support, adequate surgical debridement and broad spectrum antimicrobial therapy<sup>2,3</sup>. In early phase, it may be an empirical combination of a carbapenem or other  $\beta$ -lactam antibiotics with betalactamase and clindamycin and, in severe patients, a combination of vancomycin to cover methicillin-resistant *Staphylococcus aureus*. Clindamycin, in addition to being bacteriostatic, inhibits toxins by *Streptococcus* that could lead to cardiovascular shock<sup>3</sup>.

Clinical presentation starts seven days after contamination process. An erythematous cellulitis appears, swollen and hot, preceded by intense local pain and systemic inflammatory response syndrome (SIRS)<sup>2</sup>. The diagnosis should always be suspected when there is a disproportion between pain and clinical findings in patients with SIRS. With evolution, the erythema spreads diffusely and, in short time, dark blueish gray spots appear with blisters containing serous fluids which later turn purple. From that moment, the infection is well defined in the subcutaneous space with free cutaneous necrosis, reaching much more the fascia and adipose tissue than the cutaneous level<sup>6</sup>. The necrotic mechanism is unknown. Bacterial enzymes such as hyaluronidase might be responsible for the degradation of fascia, and lipases, for the degradation of fat tissue. Recent studies indicate that superantigens (SPE-A, SPE-B and SPE-C), secreted by certain strains of *b-hemolytic Streptococcus*, activate various cytokines, such as tumor necrosis factor alpha and beta, complement and cascade coagulation, yielding free oxygen radicals and nitric oxide, resulting in shock and failure of multiple organs<sup>7</sup>.

Necrotizing fasciitis of the breast is extremely rare. Only 16 cases are described in the literature and the majority of them has been associated with diabetes mellitus, previous invasive mammary procedures and breast cancer. In only six reports, women were not breastfeeding and had no evident risk factor<sup>1</sup>.

In the presented case, the patient had a tear in her right areola, which was probably the trigger for bacterial contamination and subsequent necrotizing fasciitis. *Streptococcus pyogenes* found in this case is in agreement with medical literature<sup>2</sup>. *Staphylococcus warneri* belongs to normal skin microbiota<sup>8</sup>. This was a type II case. Therefore, a combination of Piperacilin sodium + tazobactam sodium was prescribed aiming the coverage of *Streptococcus*, vancomycin for a possible methicillin-resistant *Staphylococcus aureus* and clindamycin, specifically for the inhibition of toxins produced by *Streptococcus*<sup>2,5</sup>.

It is important to differentiate necrotizing fasciitis of the breast in the puerperium from puerperal mastitis, especially in the early stage, when there is still no skin involvement and may erroneously be confused with puerperal mastitis. Puerperal mastitis



**Figure 3.** Parallel between the lobular duct and the focus of suppuration. Arrow detail for area of destruction and necrosis.

is the inflammatory process, infectious or not, in the breast of a breastfeeding woman<sup>9,10</sup>. It is frequent among women who breast-feed at about a 10% rate<sup>9</sup>. Risk factors include breast engorgement, scarce milk drainage, nipple excoriations or fissures, and history of previous puerperal mastitis<sup>10</sup>. The main agent is *Staphylococcus aureus* (50 to 60% of cases)<sup>9,11</sup> followed by *Streptococcus*<sup>11</sup>. Patients usually respond well to milk draining and outpatient antibiotics<sup>12</sup>.

Unlike necrotizing fasciitis, where the bacterium penetrates through a tear and affects the mammary fascia causing tissue necrosis, puerperal lactational mastitis is an infectious process secondary to the milk stasis. This leads to inflammation of the subcutaneous tissue of the breast that may undergo bacterial colonization by the flora of the mother or the newborn oropharynx<sup>13</sup>. If the breast is not promptly milked, abscess formation usually occurs within 72 hours. Even in cases where abscesses occur, studies indicate the possibility of outpatient treatment with drainage by needles or catheters<sup>14-16</sup>.

This case highlights the differential diagnosis discussed above, which is eminently clinical. The presence of necrosis and severe

pain should prompt the suspicion of necrotizing fasciitis. The prescription of antibiotics alone, without immediate debridement, augments the mortality rate. Puerperal mastitis, on the other hand, even with abscess formation, is treated successfully with antibiotics and outpatient drainage. Today's concern with breast aesthetics shouldn't halt adequate surgical debridement. Early diagnosis and appropriate therapy were fundamental for the success of treatment.

## CONCLUSION

This study describes a rare case of necrotizing breast fasciitis occurring in the postpartum period. It is essential to perform early diagnosis with differentiation from puerperal mastitis. Necrotizing fasciitis, being a serious and rapidly progressive disease where time of evolution is inversely related to survival rates, justifies the use of broad-spectrum antibiotic therapy, surgical debridement and ICU support in order to avoid further complications and death.

## REFERENCES

1. Ward ND, Harris JW, Sloan DA. Necrotizing Fasciitis of the Breast Requiring Emergent Radical Mastectomy. *Breast J*. 2017 Jan;23(1):95-9. <https://doi.org/10.1111/tbj.12686>
2. Taviloglu K, Yanar H. Necrotizing fasciitis: strategies for diagnosis and management. *World J Emerg Surg*. 2007;2:19. <https://dx.doi.org/10.1186%2F1749-7922-2-19>
3. Fayman K, Wang K, Curran R. A case report of primary necrotising fasciitis of the breast: A rare but deadly entity requiring rapid surgical management. *Int J Surg Case Rep*. 2017;31:221-4. <https://dx.doi.org/10.1016%2Fj.ijscr.2017.01.049>
4. Venkatramani V, Pillai S, Marathe S, Rege S, Hardikar J. Breast Gangrene in an HIV-Positive Patient. *Ann R Coll Surg Engl*. 2009 Jul;91(5):W13-4. <https://doi.org/10.1308/147870809X401056>
5. Kwak YG, Choi SH, Kim T, Park SY, Seo SH, Kim MB, et al. Clinical Guidelines for the Antibiotic Treatment for Community-Acquired Skin and Soft Tissue Infection. *Infect Chemother*. 2017 Dec;49(4):301-25. <https://doi.org/10.3947/ic.2017.49.4.301>
6. McAdoo GL, Monif GRG. Expanding Disease Spectrum Associated With Puerperal Mastitis. *Infect Dis Obstet Gynecol*. 1997;5(6):376-9. <https://dx.doi.org/10.1155%2F1064744997000689>
7. Green RJ, Dafoe DC, Raffin TA. Necrotizing fasciitis. *Chest*. 1996 Jul;110(1):219-29. <https://doi.org/10.1378/chest.110.1.219>
8. Kamath U, Singer C, Isenberg HD. Clinical significance of *Staphylococcus warneri* bacteremia. *J Clin Microbiol*. 1992;30(2):261-4.
9. Scott JA, Robertson M, Fitzpatrick J, Knight C, Mulholland S. Occurrence of lactational mastitis and medical management: A prospective cohort study in Glasgow. *Int Breastfeed J*. 2008;3:21. <https://doi.org/10.1186/1746-4358-3-21>
10. Sales AN, Vieira GO, Moura MSQ, Almeida SPTMA, Vieira TO. Mastite Puerperal: Estudo de Fatores Predisponentes. *Rev Bras Ginecol Obstet*. 2000 Dez [acesso em: 13 dez. 2017];22(10):627-32. Disponível em: [http://www.scielo.br/scielo.php?pid=S0100-72032000001000005&script=sci\\_abstract&tlng=pt](http://www.scielo.br/scielo.php?pid=S0100-72032000001000005&script=sci_abstract&tlng=pt) <http://dx.doi.org/10.1590/S0100-72032000001000005>
11. Beltrán Vaquero DA, Crespo Garzón AE, Rodríguez Bravo TC, García Iglesias Á. Infectious mastitis: a new solution for an old problem. *Nutr Hosp*. 2015 Feb 7;31(Supl. 1):89-95. <https://doi.org/10.3305/nh.2015.31.sup1.8714>
12. Ulitzsch D, Nyman MK, Carlson RA. Breast abscess in lactating women: US-guided treatment. *Radiology*. 2004 Set;232(3):904-9. <https://doi.org/10.1148/radiol.2323030582>
13. Betzold CM. An update on the recognition and management of lactational breast inflammation. *J Midwifery Womens Health*. 2007 Nov-Dez;52(6):595-605. <https://doi.org/10.1016/j.jmwh.2007.08.002>
14. Trop I, Dugas A, David J, El Khoury M, Boileau JF, Larouche N, et al. Breast abscesses: evidence-based algorithms for diagnosis, management, and follow-up. *Radiographics*. 2011 Out;31(6):1683-99. <https://doi.org/10.1148/rg.316115521>
15. Dixon JM. Repeated aspiration of breast abscesses in lactating women. *BMJ*. 1988 Dez 10;297(6662):1517-8.
16. Chen CY, Anderson BO, Lo SS, Lin CH, Chen HM. Methicillin-resistant *Staphylococcus aureus* infections may not impede the success of ultrasound-guided drainage of puerperal breast abscesses. *J Am Coll Surg*. 2010 Feb;210(2):148-54. <https://doi.org/10.1016/j.jamcollsurg.2009.11.003>

# NATURAL HISTORY OF DUCTAL CARCINOMA *IN SITU*

## História natural do carcinoma ductal *in situ*

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### ABSTRACT

Ductal carcinoma *in situ* (DCIS) has been detected more frequently in the last decades using the mammographic screening. The objective of the present study was to review the epidemiological aspects of DCIS. A bibliographic narrative review was carried out focusing on the following aspects: the epidemiology of DCIS to discuss subtypes; natural history; screening; and survival. It was possible to verify that the DCIS is currently considered a precursor lesion of breast cancer, presenting a considerable and uneven increased incidence between developed and developing countries, probably due to the inclusion of mammographic screening programs. There are controversies regarding the benefit or not of its detection, diagnosis, treatment and survival of patients with DCIS. It is concluded that the considerable increase in the incidence of DCIS raises an important discussion about the real need for its diagnosis as well as its real biological significance.

**KEYWORDS:** noninfiltrating intraductal carcinoma; breast neoplasms; epidemiology; incidence; carcinoma *in situ*.

### RESUMO

O carcinoma ductal *in situ* (CDIS) tem sido detectado com maior frequência nas últimas décadas a partir do rastreamento mamográfico. O objetivo do presente estudo foi revisar os aspectos epidemiológicos do CDIS. Foi realizada uma revisão bibliográfica narrativa enfocando os aspectos do CDIS: epidemiologia, para discussão a respeito dos subtipos; história natural; rastreamento; e sobrevida. Foi possível verificar que o CDIS é atualmente considerado como uma lesão precursora do câncer de mama e apresenta aumento considerável e desigual em sua incidência entre países desenvolvidos e em desenvolvimento, devido, provavelmente, à inclusão dos programas de rastreamento mamográfico. Há controvérsias quanto ao benefício ou não da detecção, do diagnóstico, do tratamento e da sobrevida de pacientes que apresentam o CDIS. Conclui-se que o aumento considerável da incidência do CDIS levanta importante discussão sobre a necessidade real de seu diagnóstico, bem como do seu real significado biológico.

**PALAVRAS-CHAVE:** carcinoma intraductal não infiltrante; neoplasias da mama; epidemiologia; incidência; carcinoma *in situ*.

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## DUCTAL CARCINOMA *IN SITU*

Ductal carcinoma *in situ* (DCIS) comprises heterogeneous lesions resulting from abnormal cell proliferation in the mammary ducts, characterized by non-invasion of the basement membrane; its differentiation from atypical ductal hyperplasia (ADH) is complex, taking into account the number of layers of proliferated cells and the wide variety of interobserver interpretation due to the proliferation of the number of cell layers<sup>1</sup>. Although a different terminology was proposed for DCIS, the World Health Organization (WHO), in their last consensus, in 2012, chose to maintain the classical nomenclature of intraductal proliferative lesions<sup>2</sup>. According to the TNM classification of the Union for International Cancer Control (UICC), DCIS is defined as Tis (DCIS) ductal carcinoma *in situ*, stage 0 (TisN0M0)<sup>3</sup>. Based on its architectural characteristics, the DCIS is classified into four morphologies: micropapillary, cribriform, solid and comedo<sup>1</sup>.

## EPIDEMIOLOGY

DCIS has been detected more frequently in the last decades, which calls the attention of medical surgeons, pathologists and researchers. Of rare occurrence in the mid-1970s, since the introduction of mammographic screening programs, it has accounted for approximately 20% of breast cancer cases detected in countries where there is organized population screening<sup>4</sup>. This increase has been most observed among women over 50 years of age (Table 1)<sup>5</sup>.

The prevalence is higher in White women, followed by Hispanic Whites, Black and Asians in the Pacific region<sup>6</sup>. The incidence of DCIS, when adjusted for age, is higher among Caucasian women, followed by African American and Asian women in the Pacific region, compared to Latin American women<sup>7</sup>. In Brazil, little information has been published on the epidemiology of carcinomas *in situ*<sup>8</sup>. It is estimated that its incidence varies between 6.6 and 8.9%<sup>9-11</sup>. In Goiânia, data from the Population-Based Cancer Registry showed a significant increase in carcinoma *in situ* cases, from 0.2 to 6.2% between 1989 and 2003<sup>10</sup>.

## MAMMOGRAPHY SCREENING

Because DCIS is not specifically screened, it is diagnosed more frequently as a consequence of screening for invasive breast cancer. As its etiology is presumably heterogeneous, prognostic evaluation based on pathology and imaging findings is highly variable<sup>12</sup>.

If, on the one hand, the mammography screening allows a considerable increase in the diagnosis of initial tumors and a substantial increase in the number of DCIS cases, on the other, this strategy of secondary prevention has also led to an increase in the so-called superdiagnosis<sup>13</sup>. This term is used for DCISs that would not evolve into the invasive variant and are nevertheless detected by screening exams<sup>14</sup>. Cases of superdiagnosis are reported more frequently on low-grade nuclear DCIS<sup>15,16</sup> in which active surveillance and individualization of treatments should be based on prospective studies<sup>13</sup>.

Although there is controversy, the benefit of the mammography screening in terms of saved lives is greater than the excess of diagnoses, since for each case of superdiagnosis, three lives are saved in groups of women submitted to the screening<sup>17</sup>.

In Brazil, the connection between the adequate mammography screening and the incidence of DCIS can be indirectly verified, with data from the population screening program in the Barretos region: there is a 20% incidence of DCIS among all tumors detected between 2003 and 2010<sup>18</sup>. Table 2 summarizes the prevalence of DCIS reported in Brazil between 2000 and 2014.

## RISK FACTORS

Regarding risk reduction factors related to breast cancer, Inumaru et al.<sup>19</sup> highlighted lactation and the practice of physical activities, both pre- and post-menopausal. The change in women's lifestyle has been indicated as an important factor related to the increase in the incidence of breast cancer<sup>20</sup>. Currently, women schedule less pregnancies, breastfeed for a shorter period, or even choose not to have children; when they do so, it usually is later on. In addition, they adopt unhealthy lifestyle habits, which lead to an increased body mass index, also considered a risk factor<sup>12</sup>. In less developed countries, the incidence of breast cancer is higher in premenopausal women, because the female population is younger and postmenopausal risk factors are not present<sup>21</sup>. Decreased use of postmenopausal hormone therapy has been suggested as responsible for the decline in the incidence of invasive breast cancer since 2003<sup>22</sup>.

For DCIS, the association with the use of hormones (estrogen and progesterone), or even an increase in the estimation of time-dependent risk, would be uncertain<sup>23</sup>. However, a study conducted in Norway involving 681 cases of DCIS, registered a 1.61% risk related to the long-term use of combinations of estrogen and progesterone<sup>24</sup>.

**Table 1.** New estimated cases of female breast cancer and deaths by age in the United States, 2013.

Age	In situ cases	Invasive cases	Deaths
<40	1,900	10,980	1,020
<50	15,650	48,910	4,780
50–64	26,770	84,210	11,970
65+	22,220	99,220	22,870
All ages	64,640	232,340	39,620

**Table 2.** Prevalence of cases of ductal carcinoma *in situ* in Brazil until 2014.

City – State	Period/year	Total of DCIS cases	DCIS prevalence (%)
São Carlos – SP	2000 to 2004	106	6.6
São Paulo – SP	2012 to 2014	288	8.1
Lavras – MG	2008 to 2013	112	8.9

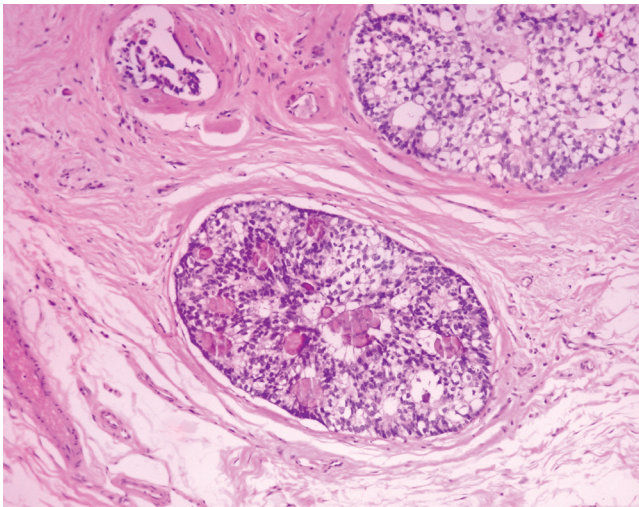
DCIS: ductal carcinoma *in situ*.

## NATURAL HISTORY

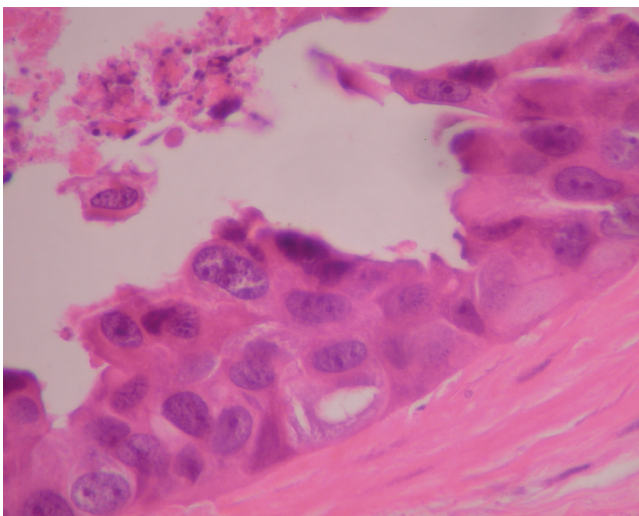
Evidence on the natural history of the progression of invading DCIS refers to different malignant changes in the ductal epithelium<sup>25</sup>, which is associated with different stages in the progression to a subsequent invasive carcinoma. However, the proportion of untreated DCIS that will develop to invasive breast cancer is unknown<sup>12</sup>.

It is observed that the cells most prone to invasion are located at the end of the duct which is regulated, preferably, by the mechanisms of adhesion and cellular contractility. During the progression of breast cancer, there are cellular morphological alterations in which the cribriform and comedo subtypes represent the final stages of DCIS<sup>26</sup>. Figures 1 to 3 illustrate the DCIS in different nuclear grades and histological subtypes.

Neoplastic cells in DCISs and in invasive ductal carcinomas show similarities at molecular levels that translate into similar



**Figure 1.** Ductal carcinoma *in situ* stage I, cribriform with foci of calcification (HE 100x).



**Figure 2.** Ductal carcinoma *in situ* stage III, comedocarcinoma (HE 400x).

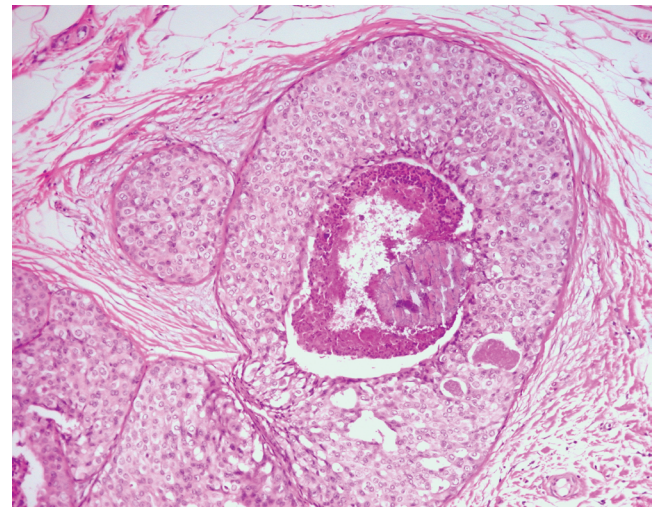
global profiles of gene and immunophenotypic expression<sup>27</sup>. The biological differences between DCIS and invasive breast carcinoma have not yet been adequately identified<sup>28</sup>, and the main known molecular phenotypes found in invasive breast cancer are similar, but different in prevalence<sup>29</sup>. Estrogen receptor expression is strongly associated with low grade DCIS, whereas HER2 overexpression is linked to high grade DCIS<sup>27</sup>.

Current evidences suggest that the transition from carcinoma *in situ* to invasive breast cancer depends on microenvironmental interactions, since the levels of change in DCIS genomic copy numbers correlate positively with the presence of immune cells, and that the invasive disease could require a number of copies leading to tumor “immunosuppression”<sup>30</sup>. The expression of tumor-infiltrating lymphocytes is higher in high-grade nuclear DCIS, with comedo necrosis, negative RE and positive HER2<sup>30</sup>.

In many cases, myoepithelial cells are abnormal presenting loss of function of tumor suppressor genes<sup>31</sup>. In addition, the interaction between stromal and epithelial cells contributes to the phenomenon of tumor cells invasion<sup>31</sup>.

## SURVIVAL

Women with a diagnosis of DCIS have high global survival rates and are close to 100%<sup>32-35</sup>, as shown in Table 3. These studies relate



**Figure 3.** Ductal carcinoma *in situ* stage II (HE 200x).

**Table 3.** Survival rates reported for women with ductal carcinoma *in situ*.

	Sagara et al., 2015 (%)	Shikama et al., 2015 (%)	Worni et al., 2015 (%)	Wadsten et al., 2016 (%)
Cancer-specific survival	98.4	91	–	97
Global survival	89.3	97	98	–



the following factors of higher local survival: low nuclear grade DCIS; conservative surgery associated with radiotherapy; and free surgical margins<sup>36,37</sup>.

The benefit of surgery for low nuclear grade DCIS is lower than in intermediate and high grade cases, compared to the results of a large study using data from Surveillance, Epidemiology, and End Results Program (SEER). Patients with low nuclear grade tumors who did not receive surgical treatment presented as little chance of evolution as those who received it, unlike women with high nuclear grade DCIS<sup>32</sup>.

In prospective studies, there are increased rates of disease-free survival in patients with DCIS who have used Tamoxifen, especially when associated with conservative surgery and radiotherapy, as well as in young patients with positive estrogen receptors<sup>36,37</sup>.

The number of invasive relapses is lower when DCIS cases are detected by screening methods compared to symptomatic DCIS, in addition to patients having longer disease-free survival<sup>37</sup>. Low recurrence rates are found in patients treated with mastectomy<sup>38</sup>.

The rates of DCIS relapse are of the order of 10 to 35%, considering risk factors: high nuclear grade; compromised margins; and women younger in age<sup>16,38,39</sup>, in this scenario about 35% occur in an invasive manner<sup>40</sup>.

From the review, there is controversy regarding the detection of DCIS. On the one hand, greater survival, on the other, superdiagnosis. Thus, it is necessary for the DCIS to be considered with special attention in order to know its natural history, which would change the understanding for its approach and reduce the need for screening.

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## REFERENCES

- Ni YB, Tse GM. Pathological criteria and practical issues in papillary lesions of the breast – a review. *Histopathology*. 2016;68(1):22-32. DOI: 10.1111/His.12866
- Gobbi H. Classificação dos tumores da mama: atualização baseada na nova classificação da organização mundial da saúde de 2012. *J Bras Patol Med Lab*. 2012;48(6):463-74.
- Sobin LH, Compton CC. TNM seventh edition: what's new, what's changed communication from the international union against cancer and the American joint committee on cancer. *Cancer*. 2010;116(22):5336-9. DOI: 10.1002/cncr.25537
- American Cancer Society. *Breast Cancer Facts & Figures 2009-2010*. Atlanta: American Cancer Society, Inc.
- DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin*. 2014;64(1):52-62. DOI: 10.3322/caac.21203
- Horner MJ, Ries LA, Krapcho M, Neyman N, Aminou R, Howlander N, et al. SEER cancer statistics review, 1975-2006. National Cancer Institute. *J Pancreas* 2010;11(2):153-6.
- Innos K, Horn-Ross PL. Recent trends and racial/ethnic differences in the incidence and treatment of ductal carcinoma in situ of the breast in California women. *Cancer*. 2003;97(4):1099-106. DOI: 10.1002/Cncr.11104
- Martins E, Freitas-Junior R, Curado MP, Freitas NM, Oliveira JC, Silva CM. Evolução temporal dos estádios do câncer de mama ao diagnóstico em um registro de base populacional no Brasil central. *Rev Bras Ginecol Obstet*. 2009;31(5):219-23. DOI: 10.1590/S0100-72032009000500003
- Macchetti AH. Estadiamento do câncer de mama diagnosticado no sistema público de saúde de São Carlos. *Medicina Ribeirão Preto*. 2007;40(3):394-402.
- Gebrim LH, Shida JY, Hegg R, Mattar TT. Avaliação do tempo de início do tratamento, estadiamento histopatológico e positividade dos biomarcadores (RE, RP, HER-2) em 3.566 pacientes tratadas pelo SUS no período de 2012 a 2014, no Hospital Pérola Byington. *Rev Bras Mastologia*. 2014;24(3):65-69. DOI: 10.5327/Z201400030002RBM
- Haddad CF. Características clínico-patológicas e estadiamento ao diagnóstico de pacientes com câncer de mama em um centro de saúde do interior de Minas Gerais. *Rev Bras Mastologia*. 2014;24(4):103-108. DOI: 10.5327/Z20140003RBM.
- Allegra CG, Aberle DR, Ganschow P, Hahn SM, Lee CN, Millon-Underwood S, et al. National institutes of health state-of-the-science conference statement: diagnosis and management of ductal carcinoma in situ. *J Nat Cancer Inst*. 2010;102(3):161-9. DOI: 10.1093/jnci/djp485
- Falk RS, Hofvind S, Skaane P, Haldorsen T. Overdiagnosis among women attending a population-based mammography screening program. *Int J Cancer*. 2013;133(3): 705-12. DOI: 10.1002/ijc.28052
- Lynge E, Ponti A, James T, Májek O, von Euler-Chelpin M, Anttila A, et al. Variation in detection of ductal carcinoma in situ during screening mammography: a survey within the international cancer screening network. *Eur J Cancer*. 2014;50(1):185-92. DOI: 10.1016/j.ejca.2013.08.013
- Kanematsu M, Morimoto M, Takahashi M, Honda J, Bando Y, Moriya T, et al. Thirty percent of ductal carcinoma in situ of the breast in Japan is extremely low-grade ER(+)/HER2(-) type without comedo necrosis. *J Med Invest*. 2016;63(3-4):192-8. DOI: 10.2152/Jmi.63.192
- Luijt PA, Heijnsdijk EA, Fracheboud J, Overbeek LI, Broeders MJ, Wesseling J, et al. The distribution of ductal carcinoma in situ (DCIS) grade in 4232 women and its impact on overdiagnosis in breast cancer screening. *Breast Cancer Res*. 2016;18(1):47. DOI: 10.1186/S13058-016-0705-5
- Ghanouni A, Meisel SF, Renzi C, Wardle J, Waller J. Survey of public definitions of the term 'overdiagnosis' in the UK. *BMJ Open*. 2016;6:e010723. DOI: 10.1136/bmjopen-2015-010723

18. Tsunoda AT, Nunes JS, Watanabe AP, Santos-Junior LA, Mauad EC, Brentani RR. Controle de qualidade em rastreamento mamográfico no Brasil: experiência do Hospital de Câncer de Barretos. *Rev Bras Mastologia*. 2013;23(1):12-18.
19. Inumaru LE, Silveira EA, Naves MM. Risk and protective factors for breast cancer: a systematic review. *Cad Saude Publica*. 2011;27(7):1259-70
20. Advani P, Moreno-Aspitia A. Current Strategies for the prevention of breast cancer. *Breast Cancer: Targets and Therapy*. 2014;6:59-71.
21. Ghiasvand R, Adami HO, Harirchi I, Akrami R, Zendehdel K. Higher incidence of premenopausal breast cancer in less developed countries; myth or truth? *BMC Cancer*. 2014;14:343. DOI: 10.1186/1471-2407-14-343
22. Kerlikowske K. Epidemiology of ductal carcinoma in situ. *J Natl Cancer Inst Monogr*. 2010;2010(41):139-41. DOI: 10.1093/jncimonographs/lgq027
23. Calvocoressi L, Stowe MH, Carter D, Claus EB. Postmenopausal hormone therapy and ductal carcinoma in situ: a population-based case control study. *Cancer Epidemiol*. 2012;36(2):161-8. DOI: 10.1016/j.canep.2012.01.001
24. Suhrke P, Zahl PH. Breast cancer incidence and menopausal hormone therapy in Norway from 2004 to 2009: a register-based cohort study. *Cancer Med*. 2015;4(8):1303-8. DOI: 10.1002/Cam4.474
25. Badruddoja M. Ductal carcinoma in situ of the breast: a surgical perspective. *Int J Surgical Oncology*. 2012;2012:12. DOI: 10.1155/2012/761364
26. Boghaert E, Radisky DC, Nelson CM. Lattice-based model of ductal carcinoma in situ suggests rules for breast cancer progression to an invasive state. *PLoS Comput Biol*. 2014;10(12):e1003997. DOI: 10.1371/Journal.Pcbi.1003997
27. Rohilla M, Bal A, Singh G, Joshi K. Prediction of heterogeneity in breast cancer immunophenotype at ductal carcinoma in situ stage? *J Cancer Res Ther*. 2016;12(4):1249-56. DOI: 10.4103/0973-1482.199541
28. Allred DC. Ductal carcinoma in situ: terminology, classification, and natural history. *J Natl Cancer Inst Monogr*. 2010;2010(41):134-8. DOI: 10.1093/jncimonographs/lgq035
29. Tamimi RM, Baer HJ, Marotti J, Galan M, Galaburda L, Fu Y, et al. Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. *Breast Cancer Res*. 2008;10(4):R67. DOI:10.1186/Bcr2128
30. Hendry S, Pang JB, Byrne DJ, Lakhani SR, Cummings MC, Campbell IG, et al. Relationship of the breast ductal carcinoma in situ immune microenvironment with clinicopathological and genetic features. *Clin Cancer Res*. 2017;23(17):5210-7. DOI: 10.1158/1078-0432.CCR-17-0743
31. Kuerer HM, Albarracín CT, Yang WT, Cardiff RD, Brewster AM, Symmans WF, et al. Ductal carcinoma in situ: state of the science and roadmap to advance the field. *J Clin Oncol*. 2009;27(2):279-88. DOI: 10.1200/JCO.2008.18.3103
32. Sagara Y, Mallory MA, Wong S, Aydogan F, DeSantis S, Barry WT, et al. Survival benefit of breast surgery for low-grade ductal carcinoma in situ: a population-based cohort study. *JAMA Surg*. 2015;150(8):739-45. doi: 10.1001/jamasurg.2015.0876
33. Wadsten C, Heyman H, Holmqvist M, Ahlgren J, Lambe M, Sund M, et al. A validation of DCIS registration in a population-based breast cancer quality register and a study of treatment and prognosis for DCIS during 20 years. *Acta Oncol*. 2016;55(11):1338-43. DOI: 10.1080/0284186X.2016.1211317
34. Shikama N, Sekiguchi K, Nakamura N, Sekine H, Nakayama Y, Imanaka K, et al. Final results from a multicenter prospective study (JROSG 05-5) on postoperative radiotherapy for patients with ductal carcinoma in situ with an involved surgical margin or close margin widths of 1 mm or less. *J Radiat Res*. 2015;56(5):830-4. DOI: 10.1093/jrr/rrv034
35. Lo AC, Truong PT, Wai ES, Nichol A, Weir L, Speers C, Hayes MM, Baliski C, Tyldesley S. Population-based analysis of the impact and generalizability of the NSABP-B24 study on endocrine therapy for patients with ductal carcinoma in situ of the breast. *Ann Oncol*. 2015;26(9):1898-903. DOI: 10.1093/annonc/mdv251
36. Qian GW, Ni XJ, Wang Z, Jiang YZ, Yu KD, Shao ZM. Effect of radiotherapy on survival of women with locally excised ductal carcinoma in situ of the breast: a surveillance, epidemiology, and end results population-based analysis. *Oncotargets Ther*. 2015;8:1407-18. DOI: 10.2147/OTT.S82087
37. Koh VC, Lim JC, Thike AA, Cheok PY, Thu MM, Tan VK, et al. Characteristics and behaviour of screen-detected ductal carcinoma in situ of the breast: comparison with symptomatic patients. *Breast Cancer Res Treat*. 2015;152(2):293-304. DOI: 10.1007/s10549-015-3472-6
38. Mathew J, Karia R, Morgan DA, Lee AH, Ellis IO, Robertson JF, et al. Factors influencing local control in patients undergoing breast conservation surgery for ductal carcinoma in situ. *Breast*. 2017;(31):181-5. DOI: 10.1016/J.Breast.2016.11.002
39. Cronin PA, Olcese C, Patil S, Morrow M, Van Zee KJ. Impact of age on risk of recurrence of ductal carcinoma in situ: outcomes of 2996 women treated with breast-conserving surgery over 30 years. *Ann Surg Oncol*. 2016;23(9):2816-24. DOI: 10.1245/S10434-016-5249-5
40. Elshof LE, Tryfonidis K, Slaets L, van Leeuwen-Stok AE, Skinner VP, Dif N, et al. Feasibility of a prospective, randomised, open-label, international multicentre, phase III, non-inferiority trial to assess the safety of active surveillance for low risk ductal carcinoma in situ - the Lord study. *Eur J Cancer*. 2015;51(12):1497-510. DOI: 10.1016/J.Ejca.2015.05.008

# NIPPLE AREOLAR RECONSTRUCTION: TECHNIQUES TO ACHIEVE A GOOD RESULT

Reconstrução do complexo aréolo papilar:  
técnicas para atingir um resultado satisfatório

Priscilla Sodré<sup>1\*</sup>, Juan Sebastian Sanches Tobar<sup>1</sup>, Roberto Vieira<sup>1</sup>, Carlos Ricardo Chagas<sup>1</sup>

## ABSTRACT

The nipple-areolar complex (NAC) reconstruction is the final touch in the reconstructive breast surgery, and it is very important for the patient's psychological health and satisfaction. There are many described techniques, but the main issue is to maintain the NAC projection over the time. The local graft reconstruction together with tattooing are the most popular techniques. However, it is important to personalize the method taking into account the patient's characteristics and the breast mound reconstruction to achieve good results. This article describes the reconstruction planning method, nipple and areolar reconstruction techniques using nipple sharing, local and autologous grafts and tattooing.

**KEYWORDS:** Nipple; mammoplasty; allografts; tattooing.

## RESUMO

A reconstrução do complexo aréolo-papilar (CAP) é o toque final da cirurgia de reconstrução mamária sendo parte importante na satisfação e saúde psicológica da paciente. Existem várias técnicas descritas, porém o maior desafio é a manutenção da projeção do mamilo ao longo do tempo. As técnicas mais utilizadas são as que utilizam enxertos locais com posterior tatuagem. Entretanto, é importante a individualização do tratamento, a técnica escolhida deve levar em consideração as características da paciente e da mama reconstruída para que o resultado final seja satisfatório. O presente artigo descreve método de planejamento, técnicas de reconstrução da aréola e do mamilo utilizando enxertos de retalho local, autólogo ou do mamilo contralateral e tatuagem.

**PALAVRAS-CHAVE:** Mamilo; mamoplastia; aloenxertos; tatuagem.

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## INTRODUCTION

The nipple-areolar complex (NAC) gives personality to the breast and, therefore, transforms a reconstructed mound into a breast. It has symbolic and aesthetic meanings. Patients with loss of NAC from cancer excision, posttraumatic events, developmental pathology and breast surgery complications experience major psychological distress. NAC reconstruction is an important and integral part of breast reconstruction and can provide significant psychosocial benefits to women.

There are many techniques described for NAC reconstruction. The goal is to create a symmetric nipple-areola complex that matches the contralateral nipple in size, color, position and projection, giving it a pleasing and natural appearance<sup>1</sup>.

Since the Adams' initial description, in the 1940s, of labial graft and nipple-areola graft, the evolution of NAC creation began<sup>2</sup>. The aim was to provide a tissue with projection. Lots of different grafts were used, like toe pulp, auricular cartilage, but the donor site morbidity was a problem<sup>3</sup>. In 1972, Millard, using a graft from the contralateral nipple, introduced the nipple-sharing concept<sup>4</sup>. The big evolution in the NAC reconstruction occurred in the 1980s, with quadropod flap, dermal fat flap, and T-flap descriptions<sup>5,6</sup>. Using the same principle, including skin grafts or not, lots of different techniques were described, including skate flap, star flap, CV flap, Bell flap, and the S-flap.

In 1986, Becker started to use the tattooing technique for NAC reconstruction, and was followed by Spear, who spread the technique. Nowadays, the high quality and several tones of pigment give it a very similar color to the original areola. Although the color match can be good, the texture and projection are lacking. Fat grafts, dermal fillers and acellular dermal matrix can be used to create better areola definition.

There is no better technique to reconstruct NAC. Each method has its own advantage and limitations, and a combination of different methods is a good choice. The most challenging problem is to maintain a satisfactory result for a long period of time. Nipple projection is most durable when the dermis of the flap is thick, and there is adequate subcutaneous tissue to reinforce the volume of the reconstructed nipple. Currently, we can also use fat grafting or dermal graft to augment an inadequate flap donor site before the definitive nipple reconstruction. Cylinders made from a naturally derived biomaterial combined with local flaps surgical techniques are an alternative for nipple reconstruction<sup>7</sup>. The decision between different methods depends on the anatomical local conditions (scars, subcutaneous tissue volume, dermis thickness, radiotherapy) and on surgeon and patient preferences.

## NIPPLE-AREOLAR RECONSTRUCTION PLANNING

Some considerations are important during the nipple-areolar reconstruction planning:

- timing: most people consider that approximately 3-5 months after reconstructive surgery is the ideal waiting time, allowing the breast position to settle as swelling resolves and gravity exerts its effect<sup>1,8</sup>. However, immediate NAC reconstruction can be performed in a patient undergoing prophylactic mastectomies with free nipple grafting when mastopexy is required. The NAC must be placed approximately 1cm medial to the midbreast line. Otherwise, they can drift laterally in the post-operative period<sup>9</sup>;
- positioning: specific landmarks can help to determine the NAC position: the level of nipple areola, the triangle with the sternal notch and the umbilicus, and the nipple-areolar position relative to each breast and the infra mammary fold. Measurements are useful to confirm the visual NAC position, but the most important item is that is simply "looks right". To help with the surgeon and patient's decision, an adhesive circle of a diameter similar to the opposite NAC can be placed in the reconstructed breast to check for the best position<sup>9</sup>. When the reconstruction is bilateral, the surgeon must use standard values to create nipple position, size, and areola size. A review of 600 breasts showed that the mean diameter of the areola is approximately 4 cm, with average nipple diameter being 1.3 cm and the average nipple projection of 0.9 cm<sup>10</sup>. The average nipple-areola and areola-breast proportion is of approximately 1.3 cm<sup>11</sup>;
- breast reconstruction technique: The loss of projection of the nipple is the big issue in its reconstruction. When the dermis is thin and there is less subcutaneous fat present, there is a great risk of nipple projection loss. Latissimus dorsi flap is the most adequate flap width, followed by less thick skin of the abdomen, and finally by the thinnest skin of the expanded mastectomy skin flap. With these issues in mind to prevent loss projection, overcorrection of 25–50% of the desired result is advised in NAC reconstruction with local flaps. Scarred areas must be avoided due to poor blood supply.

## RECONSTRUCTION TECHNIQUES

### Reconstruction of the nipple

Nowadays, surgical reconstruction is the most used method and involves the use of grafts or local flaps.

### The grafts

#### *The contralateral nipple sharing technique*

The technique was initiated by Adams, in 1944, and described by Millard in 1972. It is an excellent choice for patients with excess contralateral nipple projection, after irradiation or tissue expansion reconstruction, in which flap procedures are contraindicated. The main advantages are the perfect matching regarding color,

texture and shape between the two nipples and the long-term nipple projection<sup>12,13</sup>.

Women with average nipple length are usually more reluctant to accept this technique due to fear of contralateral surgery and the reduction of contralateral nipple sensation, although Zenn and Garofalo found that an overall patient satisfaction with the technique was 88 percent<sup>13</sup>.

The choice of donor site location depends on the nipple projection/diameter ratio. When nipple projection exceeds its diameter, sharing can be performed by “decapitation”; nipple donor tissue is removed transversely at the level of three fifths of the opposite nipple, and a small conic biopsy specimen is taken from the remaining ducts. The donor site is closed using a 6–0 absorbable purse string suture.

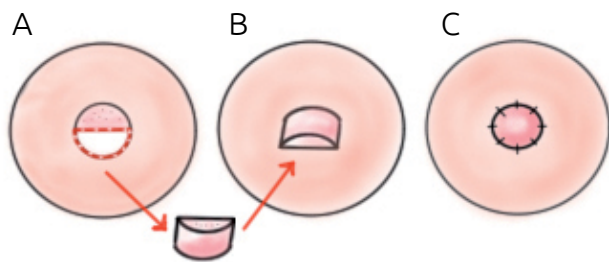
When the diameter of the nipple exceeds its height, the “vertical bipartition” is indicated; the lower half of donor nipple is marked to be folded down for donor site closure. The receptor nipple site is thinly de-epithelized using a number 15 blade. A number 11 blade is placed through the base of the nipple until its half, and then pulled upward, dividing the nipple. A small conic biopsy specimen is taken from the remaining ducts. The lower free graft is immediately placed over the de-epithelized receptor area. The center is attached to the recipient bed by a 6–0 monocryl single suture, and the periphery is closed with 5–0 multiples sutures. Non-adherent dressing and multiple Steri-Strips are used to close the area. The donor site is closed by simple approximation<sup>8</sup> (Figure 1).

### Other Grafts

Earlobe, labia minora and toe pulp are options when contralateral nipple is unavailable. They are considered “salvage full thickness grafts”. Some authors have good experiences with them<sup>14</sup>, but most think they are associated with significant donor area morbidity<sup>9</sup>.

### Local Flaps

Local flaps are currently the most commonly used techniques. The flaps can be divided, according to its design, in subdermal pedicle local flaps, such as skate flap, C-V flap, star flap,



**Figure 1.** Contralateral nipple sharing technique by “vertical bipartition”.

twin flap and centered-based local flaps, like quadrapod flap, H flap, tripod flap, mushroom flap, and the Maltesse cross flap. The main problem of these techniques is the postoperative volume loss. For this reason, many authors have advised creating a nipple that is up to twice the size of the ultimately desired volume<sup>15,16</sup>.

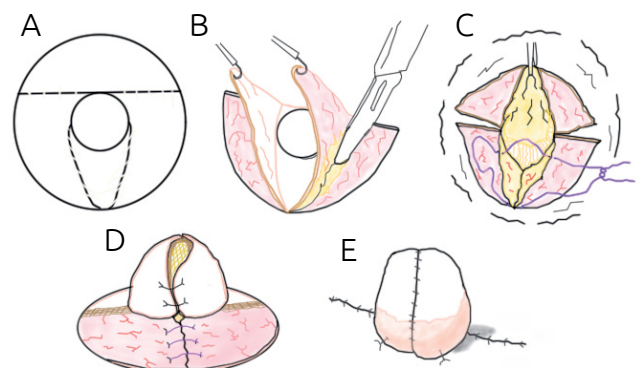
The loss of projection and volume mainly occurs because of the retraction forces of surrounding and underlying tissues, besides tissue contraction of the flap. Centered-based flaps suffer the greatest retraction forces, which act on the entire basis of the flap. Shrinking occurs to a variable degree, in all kinds of flaps. Blood supply is also a very important determinant of flap contraction, the rich subdermal plexus provides better blood supply to a subdermal pedicle flaps comparing with central pedicle flaps.

Over the years, with better understanding of local flap healing, the technique’s evolution was addressed to improving blood supply, minimizing retraction forces by simplifying flap design and by rejecting centered-based flap techniques. Enhanced vascularization was achieved by widening the subdermal pedicle base and developing double-pedicle flaps.

### Skate Flap

The skate flap nipple reconstruction was described by Little in 1984. It provides good nipple projection, diameter and definition. It uses most of the skin removed to place the areola graft<sup>17</sup>. The wings of the skate flap blood supply come from a well-vascularized subcutaneous pedicle. Women with compromised microcirculation, like heavy smokers or with irradiated breast skin are not very good candidates for this method.

This procedure reconstructs the areola and nipple. So, a circle that is equal in diameter to the contralateral areola is drawn at the NAC future site (Figure 2A). The upper third of this circle is delineated as a separate de-epithelialization, the skin is discharged. The lower two thirds will be elevated as lateral and medial wings based in the center, as an attached vascularized pedicle within the center of the circle (Figure 2B). It is



**Figure 2.** Skate flap nipple reconstruction technique.

important to provide good blood supply for the flap. The proper placement of the future nipple is determined and a 50% longer nipple projection is estimated, assuming that it will shrink to perfect symmetry. The wings of the skate flap are de-epithelialized to the proposed width of the skate flap, and then a cut through the dermis into the subcutaneous is made. This tissue is lifted up, and the wings of the flap are brought around (Figures 2B and 2C). The nipple is sutured vertically; the subcutaneous donor area is re-approximated (Figures 2D and 2E). The areolar graft can be taken from the excess tissue on the lateral portion of the mastectomy. A silicone sheet is applied to stabilize the graft, and a 10 mL syringe nipple protector is taped over the sheet for additional protection. Normally, tattooing is required and should be performed a few months later, when the nipple becomes pale.

### C-V Flap

The C-V Flap evolved from the skate flap; it is a very popular technique, which allows a medium to moderated-size nipple reconstruction with no need for an areolar graft.

After deciding the right place for the nipple, the C-V flap is designed based on the site and diameter planned for the reconstructed nipple. The diameter of the C flap will be the final nipple diameter, the height of the nipple will be correspondent to the width of the V flap, and the length of the two V flaps will correspond to the perimeter of the new nipple (Figure 3A).

Incisions are made around the two Vs and C flap. It's very important not to divide the base of the flap and leave the subdermal plexus intact to guarantee the flap's blood supply.

The two V flaps are separated from the underlying subcutaneous tissue. The flaps are thinner toward their periphery than centrally, to prevent necrosis of the tips. The C flap are also thinned, the central subcutaneous area are preserved to maintain a good blood supply for the reconstructed nipple (Figure 3B).

The initial closure involves 4-0 monocryl suture to the donor base of the C flap to the base of the V flap on both sides. The C-V flaps are positioned. The first suture secures the lowest point of the two V flaps to the center portion of the C flap's original site. The suture locks in the V flaps, and, after that, the new nipple's vertical portion is reconstructed. The tips of the V flaps are removed, their ends are sutured and the height of the nipple is reconstructed. The C flap is sutured to the upper portion of the V flaps by a single suture that grasps the tip of one V

flap in a horizontal mattress suture, (Donati), in the C flap, and goes through the other V flap. Then, the C flap is placed down onto the vertical walls of the V flap to form a cap. The donor skin is closed using a 5-0 plain catgut suture to prevent the need for suture removal (Figure 3C).

The wound dress is made with steri-trips to support the skin closure and with a nipple protector made from the back-end of a 10ml syringe barrel. This cylinder is important to prevent nipple compression by the patient's bra or clothes. Tattooing can be performed after 4-6 weeks<sup>9</sup>.

### Modified C-V flap with a dermal shelf for nipple support

This technique was developed by Jones<sup>9</sup> to prevent the retraction of the nipple, particularly in TRAM flaps, where soft fat forms the base of the nipple.

The creation of the de-epithelialized inferior dermal shelf by raising the C flap component that slides underneath the nipple at the time of donor site closure provides support to the reconstructed nipple and prevents its retrusion.

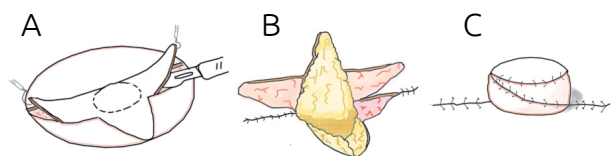
### Areolar reconstruction

Skin grafts, tattooing, purse string or a combination of these techniques can be used to reconstruct the areola. The objective and the challenge are to recreate the texture and the pigmentation of the native areola. Skin graft is usually performed at the time of nipple reconstruction. Traditionally, tattooing is performed 2-6 months after the surgical reconstruction, but some authors have shown very good results with simultaneous procedures<sup>18-20</sup>.

### Skin grafts

Many sites can be used as donor areas: skin adjacent to mastectomy scar ("dog ear"), retro auricular skin, contralateral areola and upper inner thigh. The latter became more unpopular because of donor site pain, loss of pigment over time, especially in post-menopausal women, and the possibility of hair growth on the reconstructed areola. However, upper inner thigh graft is still a good choice depending on skin color and hair growth pattern. Retro auricular graft is used solely on specific cases, when the areola is light pink. The most popular donor area for areolar reconstruction is lateral mastectomy scar, dog-ear or the lateral donor scar of the TRAM flap. However, intradermal tattoo will be necessary to provide the appropriate color<sup>9</sup>.

Donor site must be marked as an ellipse to facilitate closure. The diameter of the circle must be larger than the recipient area diameter, normally between 30-45 mm. The donor site is then closed in layers with 3/0 vicryl and 4/0 monocryl. The graft is thinned and, when necessary, all hair roots are removed using magnification loupes. The graft is transferred to the previous de-epithelialized new areolar site and is



**Figure 3.** C-V flap nipple reconstruction technique.

secured with interrupted sutures of 4/0 nylon and a running subcuticular suture of 5/0 monocril placed on the outer circumference of the areola. A hole is fashioned in the middle of the skin graft to allow the previously created nipple projection to be pulled through, creating a three-dimensional nipple complex<sup>9,21</sup>.

### Purse string suture technique

In this new technique, described by Caterson et al.<sup>22</sup>, a purse-string suture with non-absorbable suture thread is used to create areolar projection, while reducing tension on the base of the newly created nipple. Despite the small series of ten patients and the short one-year follow-up, it is a promising method to provide long-term areolar projection.

The procedure is performed under local anesthesia, about 3 months after breast reconstruction and simultaneously with nipple reconstruction. After having decided the areolar diameter, 12–15 small curvilinear (around 2 mm each) skin incisions are evenly (about 8 mm) spaced approximately 5 mm outside the desired areola diameter with an 11 blade scalpel. A double-armed 2-0 Ethibond/GoreTex or Prolene suture is then placed in either direction, through the previously created skin incisions, starting at the 12-o'clock position (Figure 4A). This is maintained relatively deep to prevent suture spitting or showing through the skin. The purse-string suture is completed at the meeting of both ends at the 6-o'clock position. The areola diameter is then cinched down to the desired measurement, thereby elevating the areola and reducing tension on the base of the nipple creation by countering the radial pull of the surrounding tissue. The curvilinear incisions are closed with 6-0 chromic sutures (Figure 4B). The NAC tattooing is performed 2 months after the purse string procedure<sup>22</sup>.

### Tattooing

Tattooing can be associated with other techniques to improve the outcome, providing the right color and shape to the reconstructed NAC. Some patients prefer this method alone, since they want the quickest, painfulness NAC reconstruction technique. Although color match and shape can be good, it lacks in

texture and projection. Nevertheless, nowadays, with 3D techniques, using principles of light and shadow to create depth on a two-dimensional surface, some tattoo artists can reproduce incredibly realistic nipple areolar complexes<sup>23</sup>.

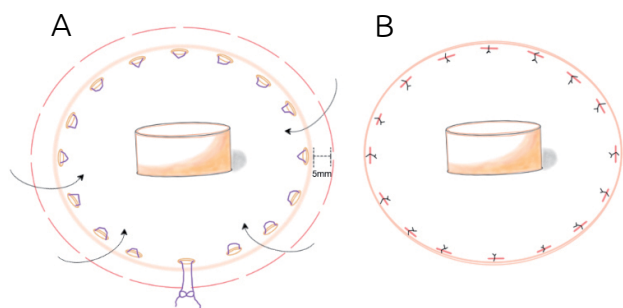
Pigment fading was the most common long-term complaint, voiced by up to 60%. After a few required touch-ups, the majority were satisfied with their outcome. Tattoo colors may be selected a bit darker to compensate the predictable changes that will occur<sup>24-26</sup>. The right technique is also very important. Pigment placed superficially will result in its extrusion and sloughing, and, if placed too deep, it will lead to macrophage ink phagocytosis, both resulting in early pigment fading<sup>25</sup>. Tattooing equipment can be regulated to ensure the right needle depth in the dermis.

### POST OPERATIVE CARE

It is very important to avoid direct pressure on the surgical site. A petroleum jelly and antibiotic ointment dressing with a circular hole cut in the center can be used to dress the wound. Some authors recommend a nipple protector made from the base of a 10 ml syringe cut with a battery-powered cautery device to provide additional nipple protection<sup>14</sup>. A standard maternity plastic nipple shield or a plastic medicine cup can be used for the same purpose. The dress should be changed often and maintained for at least two weeks after reconstruction. Hot tubs or baths must be avoided for 6–8 weeks. For patients with a graft/reconstructed areola, it is recommended to cover the areola and the nipple with petroleum jelly and antibiotic ointment dressing, and tape it securely. Wearing an appropriately fitting non-compressing bra is also advised<sup>27</sup>. Postoperative care tattooing includes dressing with non-adhesive paraffin gauze or antibiotic ointment to keep the area moistened. With desiccation, there may be a loss of pigmentation.

### CONCLUSION

There are many methods described to reconstruct the NAC and many more will be described. There are very few evidence-based studies comparing the different established methods to reconstruct the NAC, so it is difficult to conclude what the best method is. Over time, techniques have evolved and nowadays trained surgeons are able to provide long-lasting, satisfactory reconstruction with minimal morbidity. Together with expertise in the surgical technique, it is extremely important to know the patient's expectations, analyze the technical possibilities and share these possibilities and complications with the patient to decide, together, which is the best technique to be used. When the physician-patient relationship is strong, it is easier to achieve a satisfactory outcome.



**Figure 4.** Purse string suture technique to create areolar projection.

## REFERENCES

1. Nimboriboonporn A, Chuthapisith S. Nipple-Areola Complex Reconstruction. *Gland Surg.* 2014;3(1):35-42. <https://doi.org/10.3978/j.issn.2227-684X.2014.02.06>
2. Adams WM. Free transplantation of the nipples and areola. *Surgery.* 1944;15:186.
3. Klatsky SA, Manson PN. Toe pulp free grafts in nipple reconstruction. *Plast Reconstr Surg.* 1981;68:245-8.
4. Millard DR. Jr. Nipple and areola reconstruction by split-skin graft from the normal side. *Plast Reconstr Surg.* 1972;50:350-3.
5. Hartrampf CR Jr, Culbertson JH. A dermal-fat flap for nipple reconstruction. *Plast Reconstr Surg.* 1984;73:982-6.
6. Losken A, Mackay GJ, Bostwick J. Nipple reconstruction using the C-V flap technique: along term evaluation. *Plast Reconstr Surg.* 2001;108:361-9.
7. Tierney BP, Hodde JP, Changkuon DI. Biologic Collagen Cylinder with Skate Flap Technique for Nipple Reconstruction. *Plast Surg Int.* 2014;2014:ID 194087. <http://dx.doi.org/10.1155/2014/194087>
8. Nahabedian MY. Nipple reconstruction. *Clin Plast Surg.* 2007;34:131-7. <https://doi.org/10.1016/j.cps.2006.11.009>
9. Jones GE. *Bostwick's Plastic & Reconstructive Breast Surgery.* 3<sup>a</sup> ed. St. Louis, Missouri: Quality Medical Publishing; 2010.
10. Sanuki J, Fukuma E, Uchida Y. Morphologic study of nipple-areola complex in 600 breasts. *Aesthetic Plast Surg.* 2009;33:295-7. <https://doi.org/10.1007/s00266-008-9194-y>
11. Hauben DJ, Adler N, Silfen R, Regev D. Breast-areola-nipple proportion. *Ann Plast Surg.* 2003;50:510-3. <https://doi.org/10.1097/01.SAP.0000044145.34573.F0>
12. Zenn MR, Garofalo JA. Unilateral nipple reconstruction with nipple sharing: time for a second look. *Plast Reconstr Surg.* 2009 Jun;123(6):1648-53. <https://doi.org/10.1097/PRS.0b013e3181a3f2f9>
13. Adams WM. Free transplantation of the nipples and areola. *Surgery.* 1944;15:186-95.
14. Farhadi J, Maksvytyte GK, Schaefer DJ, Pierer G, Scheufler O. Reconstruction of the nipple-areola complex: an update. *J Plast Reconstr Aesthet Surg.* 2006;59:40-53.
15. Little JW. Nipple-areolar reconstruction. In: Spear SL, editor. *Surgery of the Breast: Principles and Art.* Philadelphia: Lippincott-Raven Publisher; 1998.
16. Little III J. Nipple-areola reconstruction. *Clin Plast Surg.* 1984;11:351-64.
17. Vandeweyer E. Simultaneous nipple and areola reconstruction: a review of 50 cases. *Acta Chir Belg.* 2003;103:593-5.
18. Børsen-Koch M, Bille C, Thomsen JB. Promising results after single-stage reconstruction of the nipple and areola complex. *Dan Med J.* 2013;60(10):A4674.
19. Few JW, Marcus JR, Casas LA, Aitken ME, Redding J. Long-term predictable nipple projection following reconstruction. *Plast Reconstr Surg.* 1999 Oct;104(5):1321-4.
20. Van Laeken N, Genoway K. Nipple reconstruction using a two-step purse-string suture technique. *Can J Plast Surg.* 2011;19(2):56-9.
21. Caterson SA, Singh M, Talbot SG, Eriksson E. Reconstruction of Areolar Projection Using a Purse-String Suture Technique. *Plast Reconstr Surg.* 2015 [cited on Apr 26, 2016]. Available at: [http://journals.lww.com/prsgo/Fulltext/2015/07000/Reconstruction\\_of\\_Areolar\\_Projection\\_Using\\_a.19.aspx](http://journals.lww.com/prsgo/Fulltext/2015/07000/Reconstruction_of_Areolar_Projection_Using_a.19.aspx)
22. Garg G, Thami GP. Micropigmentation: tattooing for medical purposes. *Dermatol Surg.* 2005;31:928-31; discussion 931.
23. Halvorson EG, Cormican M, West ME, Myers V. Three-dimensional nipple-areola tattooing: a new technique with superior results *Plast Reconstr Surg.* 2014 May;133(5):1073-5. <https://doi.org/10.1097/PRS.0000000000000144>
24. Wong RK, Banducci DR, Feldman S, Kahler SH, Manders EK. Pre-reconstruction tattooing eliminates the need for skin grafting in nipple areolar reconstruction. *Plast Reconstr Surg.* 1993;92(3):547-9.
25. Spear SL, Arias J. Long-Term Experience with Nipple-Areola Tattooing. *Ann Plast Surg.* 1995 Sep;35(3).
26. Hyman J, Newman M, Gayle LB. Composite syringe dressing after nipple-areola reconstruction. *Plast Reconstr Surg.* 2005;116:340-1.



# WHEN TO INDICATE RADIOTHERAPY AFTER NIPPLE-SPARING MASTECTOMY? SYSTEMATIC REVIEW

Quando indicar radioterapia após mastectomia *nipple-sparing*? Revisão sistemática

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## ABSTRACT

**Introduction:** Nipple-sparing mastectomy (NSM) and preservation of the nipple-areola complex (NAC) represent a therapeutic option of breast cancer with a better aesthetic result, a positive impact on body image and more satisfaction than the reconstruction of the NAC. It is questioned the indication of radiotherapy when the NAC is maintained and its potential aesthetic impairment. **Objective:** To examine the indication of radiotherapy in NSM and, secondarily, the incidence of NAC involvement and local recurrence rates. **Methods:** Systematic review carried out in the PubMed database with the terms (“breast neoplasm” [Mesh] OR “breast cancer”) AND (“radiotherapy” OR “radiation therapy”) AND (“nipple sparing mastectomy” OR “mastectomies” OR “subcutaneous mastectomies”). The selection of the studies, the evaluation of its quality and data extraction were carried out independently by four reviewers. **Results:** The indications for radiotherapy after NSM were: positive axilla, tumors over 5 cm and retroareolar tissue remaining greater than 5 mm. The NAC involvement occurred in 5 to 26.1% in the definitive anatomopathological study. NAC recurrence occurred from 2.59 to 10%. NAC necrosis occurred in 2.2 to 43.4%. **Conclusions:** The radiotherapy indications for NSM seem to follow the same classical indications for radiotherapy after mastectomy. The relapse index in NAC was not shown to be larger and without difference for the type of radiotherapy used. Radiotherapy should be based on factors that suggest a high risk for NAC involvement.

**KEYWORDS:** Breast cancer; radiotherapy; subcutaneous mastectomy.

## RESUMO

**Introdução:** A mastectomia *nipple-sparing* (MNS) e a conservação do complexo aréolo-papilar (CAP) representam uma manobra terapêutica do câncer de mama com melhor resultado estético, impacto positivo na imagem corporal e mais satisfação do que a reconstrução do CAP. Questiona-se a indicação de radioterapia quando da manutenção do CAP e seu potencial prejuízo estético. **Objetivo:** Examinar a indicação de radioterapia em MNS e, secundariamente, a incidência do envolvimento do CAP e as taxas de recorrência local. **Métodos:** Revisão sistemática realizada na base de dados do PubMed com os termos (“breast neoplasm” [Mesh] OR “breast cancer”) AND (“radiotherapy” OR “radiation therapy”) AND (“nipple sparing mastectomy” OR “mastectomies” OR “subcutaneous mastectomies”). A seleção dos estudos, a avaliação da qualidade do estudo e a extração de dados foram realizadas de forma independente por quatro revisores. **Resultados:** As indicações para radioterapia após MNS foram: axila positiva, tumores acima de 5 cm e tecido retroareolar remanescente maior que 5 mm. O envolvimento do CAP ocorreu em 5 a 26,1% no anatomopatológico definitivo. A recorrência no CAP ocorreu de 2,59 a 10%. A necrose do CAP ocorreu em 2,2 a 43,4%. **Conclusão:** As indicações de radioterapia para MNS parecem seguir as mesmas indicações clássicas para radioterapia após mastectomia. O índice de recidiva no CAP não mostrou ser maior com uso de radioterapia nem ter diferença quanto ao seu tipo. A decisão de realizar a radioterapia deve se basear em fatores que sugerem alto risco para envolvimento do CAP.

**PALAVRAS-CHAVE:** Câncer de mama; radioterapia; mastectomia subcutânea.

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## INTRODUCTION

Nipple-sparing mastectomy (NSM) is a surgical technique for the preservation of the nipple-areola complex (NAC) and has become a possibility of mastectomy in the treatment of breast cancer<sup>1</sup> and in risk-reducing surgery<sup>2</sup>. The aesthetic concern also arises in this new context, and this less invasive procedure protects the integrity of the NAC, whose removal may be considered an aggravating factor to the patient's mutilation feeling, as it is recognized as an attribute of femininity and identity of the breast, preserving their physical integrity<sup>3</sup>.

The conservation of the NAC brings better aesthetic result, positive impact on body image and more satisfaction than its reconstruction. However, there is concern about the risk of recurrence in NAC or the risk of a new primary breast cancer in the remaining breast tissue. This concern may have been based on initial descriptions of centripetal lymph drainage toward the subareolar plexus, as described by Sappey in 1885<sup>4</sup>.

It is questioned if the breast tissue, theoretically residual behind the NAC, should be treated with radiotherapy (RT) and what is the risk of local recurrence behind the NAC if the RT is not performed. In this scenario, it should be noted that studies are still limited to assess the role of RT in NSM<sup>1</sup>. Additional RT should play the same role as in conservative breast treatment, reducing the risk of local recurrence in the remaining breast tissue<sup>4</sup>. It should be considered that RT may bring with it considerable aesthetic impairment<sup>5</sup>. The studies do not clearly show the indications of RT when preserving NAC and what would be the best technique to be used.

The objective of this review was to evaluate the indication of RT in NSM and, secondarily, the incidence of NAC involvement and local recurrence rates.

## METHODS

A systematic review of the literature was performed in the PubMed database with the following search strategy: ("breast neoplasm" [Mesh] OR "breast cancer") AND ("radiotherapy" OR "radiation therapy") AND ("nipple sparing mastectomy" OR "mastectomies" OR "subcutaneous mastectomies") from April to June 2017, without restriction of publication date. Based on an initial research, the titles and abstracts found and the selection of the articles according to their eligibility and response criteria to the PICOS research question were followed, with P being the population (patients with breast cancer submitted to NSM); I the intervention (RT); C the comparison (no RT performing); O the outcomes (risk of local recurrence, involvement of the NAC and overall survival); and S the study/study design (randomized clinical trial and observational studies). This research was drafted in accordance with the PRISMA guidelines (Statement — Preferred Reporting Items for Systematic Reviews and Meta-Analyses)<sup>6</sup>.

The inclusion criteria were: breast cancer patients submitted to NSM followed or not by RT, criteria for indication of RT, regardless of age and gender. Exclusion criteria were: pregnant women, inflammatory breast cancer, specific populations, locoregional metastasis

and distance. The selection of the studies and the reading of the texts in their entirety were done independently by four reviewers and the articles that did not meet the eligibility criteria were excluded.

Regarding the extraction of the data of the selected articles, these were inserted in a spreadsheet of Microsoft Excel 2010, independently by four reviewers. The data selected were: author and year of publication, place of study, year of data collection, study design, sample size, age, gender, race/ethnicity, surgery indication, tumor size, location of the tumor, multicentricity, multifocality, positive axillary lymph nodes, criteria for RT indication, RT rate, follow-up, molecular classification, NAC involvement, NAC recurrence rate, NAC necrosis, histological subtype and association measure.

The quality of the studies was evaluated using the critical evaluation tools for studies of the Joanna Briggs Institute<sup>7,8</sup>. For cohort studies, the tool assesses, through 11 questions, items such as similarity between groups, exposure and outcome measures, strategies for confounding control, absence or non-outcome at the beginning of the follow-up of the participants, follow-up time, and statistic. For the case series, the tool evaluates ten questions about inclusion criteria, method, characteristics of participants, follow-up and statistical analysis. Each question may be answered with "yes", "no", "uncertain" and "not applicable". The study with more "yes" answers is more likely to be of good quality, and, arbitrarily, those with scores between 0 and 3 are considered poor, between 3 and 6 are reasonable and those between 7 and 11 have good or high quality. The reviewers independently assessed the quality of each study. Disagreements were solved by consensus.

## RESULTS

### Selection of studies

A total of 223 articles were retrieved in the database search. After the screening of titles and abstracts, 19 full-text articles were read and evaluated for eligibility. In the end, 13 articles were considered for the systematic review due to their answering the research's question. Eligible studies were published between 2005 and 2017 and with collection period from 1980 to 2015. Figure 1 shows a flow diagram of the article selection process.

### Studies and characteristics of participants

Four prospective cohorts<sup>2,3,9,10</sup>, two retrospective ones<sup>11,11</sup> and seven case series<sup>4,5,12-16</sup> were included, totaling 5,781 individuals. The studies collected had mean follow-up periods ranging from 13 months to 13 years. In most studies, women represented the largest proportion of the sample<sup>2,4,5,12-16</sup>. The mean age was 44 to 52 years<sup>10,16</sup>. Only one work<sup>1</sup> mentions race/ethnicity, being 82% white, 42.9% black and 36.8% Asian. Table 1 shows the characteristics of the studies.

### Result definitions

The tumor size considered was T2<sup>1-3,5,10,14</sup>. The central location of the tumor was reported in 3 studies<sup>2,3,9</sup>, considering distances for

NAC<sup>2</sup> greater than 2.5 cm and at least 1 cm of the areola<sup>3,9</sup> for its conservation. The indications for surgery were: multifocal, multicentric tumor, extensive intra-ductal carcinoma *in situ* (DCIS)<sup>15</sup>, bilateral cancer<sup>3</sup>, diffuse microcalcifications distant from NAC, negative intraoperative retroareolar freezing<sup>16</sup> and prophylactic mastectomy<sup>2</sup>. Positive armpit was found in the frequency of 13 to 40.74%<sup>1-4,10,11,13-16</sup>. The indications for RT after NSM were: positive axilla, tumors<sup>1</sup> over 5 cm and remaining retroareolar tissue<sup>2</sup> greater than 5 mm. Survival considered in the follow-up period was 100, 97<sup>1</sup> and 76.4%. NAC involvement occurred in 5 to 26.1%<sup>2,4,9,10,12,14-16</sup> in the definitive anatomopathological study. Recurrence in the NAC occurred in 2.59 to 10%<sup>2,3,9,10,14-16</sup>. CAP necrosis occurred in

2.2 to 43.4%<sup>2-5,9,12,16</sup>. The most frequent histological subtypes were infiltrating ductal carcinoma (IDC) and DCIS, with the following percentages: 56 to 82%<sup>1-3,9,10,16</sup> and 9.26 to 40%<sup>1-3,9,10,16</sup>, respectively. The molecular classification represented 29 to 89.2% of positive estrogen receptor<sup>1,2,10,11,14,16</sup>, from 17.16 to 79.7% of HER-2 positive<sup>2,16</sup> and 6.25% of triple negative<sup>13</sup>. The rate of RT in NAC was 16.6 to 100%<sup>1-3,9-11,13,15,16</sup>. The studies did not provide an association measure for overall and disease-free survival.

## Evaluation of the quality of the articles

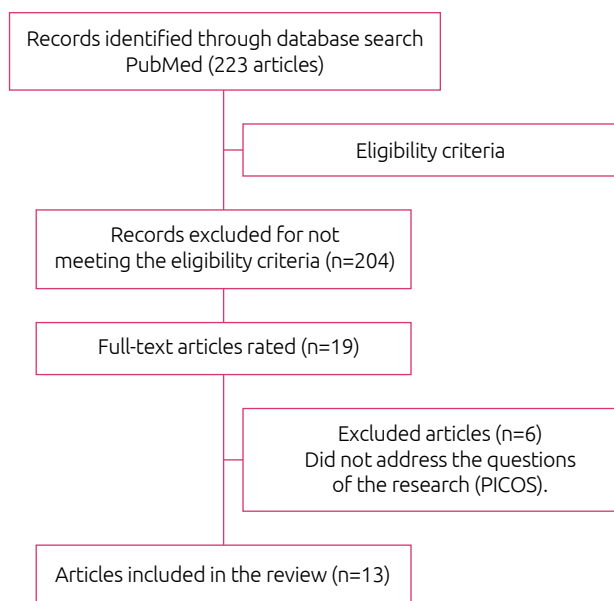
The case series showed scores, according to the JBI, averaging 7 to 8 “yes” answers for 6 rated articles and 6 for 1 article. The cohorts presented 6 studies with scores above 7 and 2 studies with scores 5 and 6 (because they did not adequately describe about follow-up and about how they dealt with confounding factors).

## DISCUSSION

### Radiotherapy: indications and complications

Because NSM is an approach that preserves the glandular tissue behind the areola to protect the vascularization of the NAC, postoperative RT could complement this treatment, reducing the risk of local recurrence. However, the use of radiation in patients submitted to NSM is variable in the literature<sup>9</sup>. In the present study, the rate of RT in NAC was from 16.6 to 100%, showing a high variability of indication among the studies.

The indications for RT after NSM identified in the present review were positive axilla, tumors over 5 cm and retroareolar tissue remaining greater than 5 mm. Such indications are similar to the general RT recommendations in breast cancer patients undergoing mastectomy and suggest that indications are for



**Figure 1.** Flow diagram of the selection process.

**Table 1.** Characteristics of the studies.

Author	Year	Period of data collection	Country	Sample size	Design of the study
Agarwal et al. <sup>2</sup>	2014	2005 to 2009	United States	449	Retrospective cohort
Rulli et al. <sup>3</sup>	2013	2003 to 2011	Italy	77	Prospective cohort
Petit et al. <sup>4</sup>	2009	2002 to 2007	Italy	1,001	Prospective cohort
Reish <sup>10</sup>	2015	2007 to 2012	United States	45	Case series
Petit et al. <sup>11</sup>	2009	2002 to 2007	Italy	579	Case series
Benediktsson e Perbeck <sup>13</sup>	2008	1988 to 1994	Sweden	216	Prospective cohort
Cont et al. <sup>14</sup>	2017	2010 to 2015	Italy	518	Case series
Petit et al. <sup>16</sup>	2005	2002 to 2003	Italy	106	Case series
Agarwal e Argawal <sup>18</sup>	2015	2006 to 2010	United States	470	Case series
Petit et al. <sup>19</sup>	2005	2002 to 2005	Italy	333	Prospective cohort
Coopey et al. <sup>20</sup>	2013	2007 to 2013	United States	97	Case series
Cho et al. <sup>21</sup>	2015	2005 to 2014	Korea	85	Case series
Horiguchi <sup>22</sup>	2006	1980 to 2001	Japan	1,574	Retrospective cohort

high risk patients, such as those with tumors larger than 5 cm, positive axillary lymph nodes and positive margins. The results of recent trials on local RT extended these indications to intermediate risk patients (high risk with negative lymph nodes and 1 to 3 positive lymph nodes)<sup>9</sup>.

According to Marta et al.<sup>17</sup>, the opinions of radiotherapists and breast surgeons on the indications of RT for patients submitted to NSM and skin-sparing mastectomy were evaluated. Questionnaires with 22 questions were sent to radiotherapists and breast surgeons from North America, South America and Europe. A total of 550 physicians (298 radiotherapists and 252 breast surgeons), being 41.64% from South America, 29.45% from North America and 25.82% from Europe, answered the survey, and although they disagree on some aspects, with statistically significant differences, there was agreement that RT should be performed on early stage breast cancer (I and II) for patients presenting risk factors for local recurrence. Although there is some disagreement among the interviewees, the standard risk factors for relapses considered important between the two specialties are: age under 40 years, involvement of 1 affected lymph node (radiotherapists) or 3 lymph nodes (breast surgeons), tumor greater than 5 cm, extracapsular extension, compromised margins, lymphatic invasion, triple negative and multicentric tumors. Values between 1 and 5 mm were considered acceptable for residual mammary tissue. In cases of initial cancer (stage 0 to II), skin-sparing mastectomy is not associated with decreased systemic and locoregional control. This is not the case for more advanced tumors, which may reach 31% local recurrence compared to 5.8% in tumors with stage 0 to II. The most significant features for local recurrence are: lymph node involvement, tumor size, degree of tumor differentiation, and lymphovascular invasion<sup>17</sup>.

Thus, the indication of RT after NSM seems to follow the usual indications of RT after mastectomy and considers the associated risk factors, however, does not appear to be a consensus. This can be verified according to Agarwal and Agarwal, who evaluated in the literature whether patients submitted to NSM were more likely to receive RT. A total of 112,817 patients were submitted to NSM (470 patients, 0.4%) and to other forms of mastectomy (112,347; 99.6%) from 2006 to 2010. Patients submitted to NSM had higher RT rates than patients submitted to other forms of mastectomy in paired comparisons, taking axillary status and tumor size into account. RT was performed in 18% of patients submitted to NSM and did not meet the criteria established by the National Comprehensive Cancer Network (NCCN), compared to 6% in the group of other types of mastectomy<sup>18</sup>. This behavior of a certain tendency to indicate RT simply because of the maintenance of the NAC still needs to be reviewed and a consensus must be established in international protocols regarding the standard conduct in these cases.

Some discussion points related to post-NSM RT refer to the local complications associated with it: NAC necrosis, capsular contraction and deviation of the NAC position influence the final aesthetic

result of the reconstructions. In a retrospective study, Reish et al. evaluated 605 immediate breast reconstructions made after NSM. Of these, 88 were treated with RT. There was a trend towards more complications in patients submitted to RT (19.3 *versus* 12.8%;  $p=0.099$ ) associated with a higher risk of implant loss (6.8 *versus* 1.0%;  $p=0.001$ ). Preoperative RT had a higher risk of total complications — with  $p=0.04$ ; *odds ratio* (OR) 2.225; and 95% confidence interval (95%CI), 1.040–4.758 —, and postoperative RT had a higher risk of extrusion ( $p=0.015$ , OR = 5.634, 95%CI, 1.405–22.603). There was no significant difference in the need for NAC removal due to poor positioning or positive cancer margins in irradiated patients compared to non-irradiated patients. The irradiated patients had a higher incidence of secondary procedures due to capsular contracture (12.5 *versus* 2.3%;  $p<0.001$ ) and steatonecrosis (13.6 *versus* 3.9%;  $p<0.001$ ). The total success rate for NAC preservation was 90% (79 out of 88) and the rate of reconstruction failure was 8%<sup>10</sup>.

The results of another study, a meta-analysis by Zheng et al., indicate that the rate of occurrence of NAC necrosis and local recurrence is the same among patients who received and the ones did not receive RT, however, cutaneous necrosis is more common in irradiated patients<sup>15</sup>. Such possible complications should begin to be taken into account, since there currently seems to be more flexibility to indicate RT when NSM is performed, even in situations where it would not radiate if the NAC had been removed.

### Involvement of the areola-papillary complex

Gomez et al. reviewed NSM publications focusing on the incidence of NAC involvement in post-surgery recurrence rates and on post-NSM RT data. The reported rate of NAC involvement ranged from 0 to 58%. The factors most commonly associated with NAC involvement were: clinical suspicion of NAC involvement, tumor distance to CAP (<2 cm), tumor size (>2 cm), location of the primary tumor in the central quadrant of the breast, multicentricity/multifocality and axillary lymph node involvement<sup>1</sup>. In the present study, the NAC involvement rate was 5 to 26.1% in the definitive anatomopathological study.

Agresti et al. evaluated 422 patients submitted to NSM, of whom 61 were referred to neoadjuvant chemotherapy (QT-neo). The compromised NAC, seen during intraoperative and/or in the histological final freezing, in the NSM group and the NSM-post chemotherapy was seen, respectively, in 48 of 361 cases (13.3%) and in 6 of 61 cases (9.8%). Of the 54 patients with NAC commitment, 51 were submitted to resection of the NAC and 3 to the RT, according to the patient's desire to preserve the NAC. The three patients did not present local recurrence. Of the 51 patients who underwent NAC removal, residual disease was found in 21 of them (5 IDC and 16 DCIS), with no significant difference between those who underwent QT-neo and those who did not<sup>12</sup>. Benediktsson et al., in a series of 272 patients submitted to NSM and retroareolar freezing, observed that the sensitivity of freezing was 90.9% and the specificity was 98.5% in the assessment of retroareolar

involvement by the disease<sup>13</sup>. Intraoperative freezing seems to be a safe method for deciding whether or not to preserve the NAC according to the data evaluated.

### Local recurrence after nipple-sparing mastectomy

In addition to total or partial necrosis of NAC and loss of sensitivity, local recurrence is one of the major concerns when thinking about NSM. In the series of 272 patients submitted to NSM evaluated by Benediktsson et al., only 47 received RT. Among the irradiated patients, the locoregional recurrence rate (LRR) was 8.5% after 13 years. In that study, the occurrence of LRR after NSM was independent of staging and lymph node status and did not affect overall survival. Late LRR (after three years) had a better prognosis than the initial ones. The frequency of LRR, according to the authors, can be substantially reduced by RT<sup>13</sup>.

The study by Petit et al. concluded that the local recurrence rate in NSM with RT was not higher than that observed in the literature after conventional mastectomies and the preservation of NAC would not increase this risk<sup>16</sup>. In a series of 137 cases evaluated, the patients underwent intraoperative RT (intraoperative single electron dose radiotherapy – ELIOT) and the NAC was preserved even when the freezing of the retroareolar tissue was positive. Two local recurrences (1.5%) were observed, both located at least 2 cm away from the areola. One of the patients who had recurrence had a positive DCIS retroareolar histology, however, there was no recurrence in NAC in 18 patients with persistent positive histology<sup>19</sup>. NAC recurrence occurred in 2.59 to 10% in the present review and literature data show a relatively small relapse rate, which may suggest oncological safety in the indication of NSM in low risk patients.

Cont et al., in a series with 518 patients, observed that recurrences after NSM almost invariably occurred in the subdermal tissue of the flap that covered the tumor area rather than the NAC. In this series, the high degree and the high rate of tumor proliferation, both in invasive and in situ tumors, were significantly associated with local recurrence, whereas no recurrence occurred in cases submitted to RT. Thus, according to the authors, it is assumed that in selected patients submitted to NSM, the partial RT of the thoracic wall directed to the primary tumor's quadrant may be associated with the same reduction of recurrences as the RT of the whole breast, reducing thus complications in reconstruction<sup>14</sup>. Similar results were found by Petit et al. in a series of 579 patients, in which they found a recurrence rate of 0.9% per year, with the majority of recurrences occurring in the tumor site and not in the NAC<sup>11</sup>. Thus, the NAC should not always be the target of adjuvant RT.

Rulli et al. prospectively evaluated 77 patients who underwent NAC sparing mastectomy between 2003 and 2011. Patients aged between 18 and 75 years, those with a diagnosis of DCIS or IDC with a size smaller than 2.5 cm, with distance from the tumor with CAP greater than 2.5 cm, with lesion not located in the central quadrant of the breast, without bloody papillary discharge, without cutaneous

involvement, with indication of mastectomy due to multifocal disease or diffuse microcalcifications and negative intraoperative histological evaluation of the retroareolar region. Patients with inflammatory carcinoma, those submitted to QT-neo, and those with Paget's carcinoma were excluded. During the follow-up of these patients (mean of 55 months), 2 locoregional recurrences were observed in NAC, which were treated with surgical removal of the NAC at 33 and 37 months of follow-up<sup>3</sup>. The safety of the NSM is also supported by the distance of the tumor to the NAC and the distance limit of 2.5 cm seems to be indicated for the oncological safety of NAC preservation.

Petit et al. described the results of 1,001 patients submitted to NSM, and 800 received the ELIOT technique of intraoperative RT of NAC and 201 received late RT. The mean follow-up of 20 months showed 3.5% total NAC necrosis, 5.5% partial necrosis, and 5% of the cases required surgical removal. There were 2% of infections and 4.3% of the prostheses were removed. Partial sensitivity of preserved NAC was reported by 15% of patients. Of the 14 cases of recurrence (1.4%), 10 occurred in an area near the site of the primary tumor, all distant from the irradiated NAC. There was no recurrence in the NAC. There were, in general, 36 cases of metastatic diseases with four deaths. The fact that there was no recurrence in NAC is a strong argument in favor of the efficacy of RT in NAC even with a short follow-up of patients<sup>4</sup>, however, one should wait for the result of a longer follow-up and that a randomized and prospective study comparing NSM with or without RT in the NAC is performed, since other works that did not perform RT also have low recurrence rates in the CAP at follow-up.

### Limitations and strengths of the present study

The evaluation of the quality of articles according to JBI showed that the case series appeared to be of good to high quality, with an average of 7 to 8 "yes" answers for 6 articles evaluated and 6 for 1 article of reasonable quality. Cohorts presented good and high quality for 6 studies with scores above 7 and reasonable quality for 2 studies with scores 5 and 6. This result indicates that the studies included in this review have a low risk of bias and have adequate data reliability, according to critical evaluation items, with most of them identifying confounding factors and appropriate statistical analysis.

It was not possible to perform a meta-analysis on RT in NAC after NSM, local recurrence after NSM and global and disease-free survival due to different study models between selected articles and lack of adequate association measure.

### CONCLUSION

NSM, after negative retroarticular freezing and following the appropriate indication criteria, appears to be oncologically safe in the treatment of breast cancer, as long as the tumor is not close to the CAP and the retroareolar tissue has adequate thickness. Intraoperative freezing is a safe method of deciding whether or not the NAC should be preserved.

The indications of RT for NSM appear to follow the same classical indications for RT after mastectomy and the rate of relapse in NAC has not been shown to be larger with or without RT and no difference for the type of RT used. Only the achievement of NSM is an inadequate justification for RT post-mastectomy. The decision to perform RT should be based on preoperative

imaging, clinical factors or pathological findings that suggest a high risk for NAC involvement. Although adjuvant RT is not an absolute contraindication in NSM, it should be used with caution as it decreases the final cosmetic result.

Prospective studies should be performed to adequately assess local recurrence rates in NAC after NSM with or without RT.

## REFERENCES

- Gomez C, Shah C, McCloskey S, Foster N, Vicini F. The Role of Radiation Therapy after Nipple-Sparing Mastectomy. *Ann Surg Oncol*. 2014;21:2237-44. <https://doi.org/10.1245/s10434-013-3446-z>
- Agarwal S, Agarwal S, Neumayer L, Agarwal JP. Therapeutic nipple-sparing mastectomy: trends based on a national cancer database. *Am J Surg*. 2014;208:93-8. <https://doi.org/10.1016/j.amjsurg.2013.09.030>
- Rulli A, Caracappa D, Barberini F, Boselli C, Cirocchi R, Castellani E, et al. Oncologic Reliability of Nipple-sparing Mastectomy for Selected Patients with Breast Cancer. *In Vivo*. 2013;27:387-94.
- Petit JY, Veronesi U, Orecchia R, Rey P, Martella S, Didier F, et al. Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European institute of oncology of Milan (EIO). *Breast Cancer Res Treat*. 2009;117:333-8. <https://doi.org/10.1007/s10549-008-0304-y>
- Boyer MR. La mastectomia ahorradora de piel como alternativa a la mastectomia estándar em el cáncer de mama. *Cir Esp*. 2008;84(4):181-7. [https://doi.org/10.1016/S0009-739X\(08\)72617-4](https://doi.org/10.1016/S0009-739X(08)72617-4)
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009;6(7):1-6. <https://doi.org/10.1371/journal.pmed.1000097>
- Joanna Briggs Institute. Critical Appraisal Checklist for Cohort Studies [Internet]. Austrália: Joanna Briggs Institute; 2016 [acesso em: 10 out. 2017]. Disponível em: <http://joannabriggs.org/research/critical-appraisal-tools.html>
- Joanna Briggs Institute. JBI Critical Appraisal Checklist for Case Series [Internet]. Austrália: Joanna Briggs Institute; 2016 [acesso em: 10 out. 2017]. Disponível em: <http://joannabriggs.org/research/critical-appraisal-tools.html>
- Orecchia R. The use of postoperative radiation after nipple sparing mastectomy. *Orecchia. Gland Surg*. 2016;5(1):63-8. <https://dx.doi.org/10.3978%2Fj.issn.2227-684X.2015.11.01>
- Reish RG, Lin A, Phillips NA, Winograd J, Liao EC, Cetrulo CL Jr, et al. Breast Reconstruction Outcomes after Nipple-Sparing Mastectomy and Radiation Therapy. *Plast Reconstr Surg*. 2015;135:959-66. <https://doi.org/10.1097/PRS.0000000000001129>
- Petit JY, Veronesi U, Rey P, Rotmensz N, Botteri E, Rietjens M, et al. Nipple-sparing mastectomy: risk of nipple-areolar recurrences in a series of 579 cases. *Breast Cancer Res Treat*. 2009 Mar;114(1):97-101. <https://doi.org/10.1007/s10549-008-9968-6>
- Agresti R, Sandri M, Gennaro M, Bianchi G, Maugeri I, Rampa M, et al. Evaluation of Local Oncologic Safety in Nipple Areola Complex-sparing Mastectomy After Primary Chemotherapy: A Propensity Score-matched Study. *Cancer*. Clin Breast Cancer. 2017;17(3):219-31. <https://doi.org/10.1016/j.clbc.2016.12.003>
- 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 Feb;34(2):143-8. <https://doi.org/10.1016/j.ejso.2007.06.010>
- Cont NT, Maggiorotto F, Martincich L, Rivolin A, Kubatzki F, Sgandurra P, et al. Primary tumor location predicts the site of local relapse after nipple-areola complex (NAC) sparing mastectomy. *Breast Cancer Res Treat*. 2017;165:85-95. <https://doi.org/10.1007/s10549-017-4312-7>
- Zheng, Zhong M, Ni C, Yuan H, Zhang J. Radiotherapy and nipple-areolar complex necrosis after nipple-sparing mastectomy: a systematic review and meta-analysis. *Yajuan Radiol Med*. 2016;122:171-8. <https://doi.org/10.1007/s11547-016-0702-x>
- Petit JY, Veronesi U, Orecchia R, Luini A, Rey P, Intra M, et al. Nipple-sparing mastectomy in association with intra operative radiotherapy (ELIOT): A new type of mastectomy for breast cancer treatment. *Breast Cancer Res Treat*. 2006 Mar;96(1):47-51. <https://doi.org/10.1007/s10549-005-9033-7>
- Marta GN, Poortmans P, Barros AC, Filassi JR, Freitas Junior R, Audisio RA, et al. Multidisciplinary international survey of post-operative radiation therapy practices after nipple-sparing or skin-sparing mastectomy. *Eur J Surg Oncol*. 2017 Sep 19;43:2036-43. <https://doi.org/10.1016/j.ejso.2017.09.014>
- Agarwal S, Agarwal J. Radiation Delivery in Patients Undergoing Therapeutic Nipple-Sparing Mastectomy. *Ann Surg Oncol*. 2015;22:46-51. <https://doi.org/10.1245/s10434-014-3932-y>
- Petit JY, Veronesi U, Luini A, Orecchia R, Rey PC, Martella S, et al. When mastectomy becomes inevitable: the nipple-sparing approach. *The Breast*. 2005 Dez;14(6):527-31. <https://doi.org/10.1016/j.breast.2005.08.028>
- Coopey SB, Tang R, Lei L, Freer PE, Kansal K, Colwell AS, et al. Increasing eligibility for nipple-sparing mastectomy. *Ann Surg Oncol*. 2013 Oct;20(10):3218-22. <https://doi.org/10.1245/s10434-013-3152-x>
- Cho JW, Yoon ES, You HJ, Hyon-Surk Kim HS, Lee BI, Park SH. Nipple-areola complex necrosis after nipple sparing mastectomy with immediate autologous breast reconstruction. *Arch Plast Surg*. 2015 Sep;42(5):601-7. <https://doi.org/10.5999/aps.2015.42.5.601>
- Horiguchi J, Koibuchi Y, Yoshida T, Takata D, Kikuchi M, Rokutanda N, et al. Significance of local recurrence as a prognostic factor in the treatment of breast cancer. *Anticancer Res*. 2006;26:569-74.

# INSTRUCTIONS TO AUTHORS

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The selection of themes is based on planning established by the Editor-in-Chief and Co-Editors. Articles in this category are usually ordered by publishers from authors with proven experience in the field. Spontaneous contributions may be accepted. It must present: Title, Abstract (without need of structuring), Keywords, Text (with or without subtitles), and References. The general instructions for figures, tables and references are the same as for the original articles.

**Images in Mastology:** Unusual images in clinical practice or associated with topics which are considered as rare. The text will be continuous, expressing the rarity or singularity of the case, at maximum of 400 words, and no more than 10 references and 3 figures. They must present: Title, Abstract (non-structured up to 150 words), Keywords, and References.

**Case reports:** They are manuscripts reporting unpublished, highly interesting and well-documented clinical cases from a clinical and laboratorial point of view. The text should express the rarity or singularity of the case, at maximum of 2,000 words, and no more than 20 references and 3 figures. They should observe the structure: Introduction, Case report (with patient description, results of clinical exams, follow-up, diagnosis), Discussion (with similarity data in the literature), and Conclusion. They must present: Abstract (unstructured), Keywords, and up to 20 References.

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- Title of the article, in Portuguese and English, containing between 10 and 12 words, without articles and prepositions. The Title should be motivating and should give an idea of the objectives and content of work;
- full name of each author, without abbreviations;
- indication of the academic degree and institutional affiliation of each author, separately. If there is more than one institutional affiliation, indicate only the most relevant;
- indication of the Institution where the work was done;
- name, address, fax and e-mail of the corresponding author;
- sources of research assistance, if any;
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### B) Second sheet

**Abstract and Descriptors:** Abstract, in Portuguese and English, with a maximum of 250 words. For The original articles, should be structured (Objective, Methods, Results, Conclusions), highlighting the most significant data of the work. For case reports, revisions or updates and a previous note, the summary should not be structured. Below the abstract, specify at least five and at most ten descriptors (Keywords) that define the subject of the work. The descriptors should be based on the DECS – Descriptors in Health Sciences – available at <http://www.decs.bvs.br>

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You should strictly obey the structure for each category of manuscript.

In all manuscript categories, the citation of the authors in the text should be numeric and sequential. Using Arabic numerals in parentheses and envelopes.

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## Presentation of the text

Preferably use the Microsoft Word® word processor.

Do not emphasize excerpts from the text: do not underline and do not use bold. Do not use capital letters in proper nouns (other than the first letter) in the text or Bibliographical References. When using acronyms or abbreviations, describe them in full the first time they are mentioned in the text.

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The Summary should contain the relevant information, allowing the reader to get a general idea of the work. All articles submitted must have a summary in Portuguese or Spanish and in English (abstract), between 150 and 250 words. For Original Articles, abstracts should be structured including objectives, methods, results and conclusions. For the other categories, the format of the abstracts may be the narrative, but preferably with the same information. They should not contain quotations and abbreviations. Highlighting at least three and at most six indexing terms, extracted from the vocabulary "Descriptors in Health Sciences" (DeCS – [www.bireme.br](http://www.bireme.br)), when accompanying the abstracts in Portuguese or Spanish, and Medical Subject Heading – MeSH (<http://www.nlm.nih.gov/mesh/>), when they follow the "Abstract". If no descriptors are available to cover the subject of the manuscript, terms or expressions of known use may be indicated.

## Introduction

In this section, show the current state of knowledge about the topic under study, divergences and gaps that may possibly justify the development of the work, but without extensive review of the literature. For Case Reports, present a summary of the cases already published, epidemiology of the reported condition and a justification for the presentation as an isolated case. Clearly state the objectives of the work.

## Methods

Start this section indicating the work planning: whether prospective or retrospective; Clinical or experimental trial; Whether the distribution of cases was random or not, and

so on. Describe the criteria for selection of patients or experimental group, including controls. Identify the equipment and reagents used. If the applied methodology has already been used, give the references in addition to the brief description of the method. Also describe the statistical methods employed and the comparisons for which each test was used. In the Case Reports, the sections Material and Methods and Results are replaced by the description of the case, remaining the remaining cases.

## Results

It should be limited to describing the results found without including interpretations and comparisons. Present the results in logical sequence, with text, tables and figures.

## Discussion

It should properly and objectively explore the results, discussed in light of other observations already recorded in the literature, highlighting the new and original information obtained in the research. Emphasize the appropriateness of the research methods used. Compare and relate the observations with those of other authors, commenting and explaining the differences that occur. Explain the implications of the findings, their limitations, and make recommendations. The discussion should culminate with the conclusions, indicating ways for new research or implications for professional practice. For Case Reports, base the Discussion on a broad and updated literature review.

## Thanks

Collaborations of individuals, institutions or acknowledgments for financial support, technical aids, deserving recognition, but not justifying inclusion as the author, should be included.

## References

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### Articles of Journals or Magazines

Del Giglio A, Pinhal MA. Genetic profile in breast cancer: a brief review for the mastologist. *Rev Bras Mastologia*. 2005; 15 (1): 45-50.

### My Account

Montoro AF. *Mastology*. São Paulo: Sarvier, 1984.

### Book Chapters

Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap III LC, Wenstrom KD. *Williams Obstetrics*. 22nd ed. New York: McGraw-Hill; 2005. Chapter 39, Multifetal gestation. P. 911-43.

### With authorship

Von Hoff DD, Hanauske AR. Preclinical and early clinical development of new anti-cancer agents. In: Kufe DW, Bast RC Jr, Hait WN, Hong WK, Pollock RE, Weichselbaum RR, et al. Editors. *Holland-Frei cancer medicine*. 7th ed. Hamilton (ON): BC Decker Inc.; 2006. p. 600-16.

### Theses and Dissertations

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

## Electronic publications

Henrique MA, Cosiski MHR. Mammographic density as a risk factor for breast cancer. *Rev Bras Ginecol Obstet* [Internet]. 2007 [cited 2008 Feb 27]; 29 (10): 493-6.

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