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ORIGINAL ARTICLE

Axillary web syndrome is not a risk factor for lymphoedema after 10 years of follow-up

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Abstract
Objective The objective of this study was to evaluate the association between axillary web syndrome and the development of lymphoedema after 10 years of follow-up.
Methodology A prospective observational study in a hospital cohort of women diagnosed with breast cancer and treated at a referral centre for cancer. Patients were followed according to the routine of the hospital's physical therapy service. In addition, a review of medical records was conducted for the period between 5 and 10 years of follow-up. Data on patient characteristics, treatment, tumour and postoperative complications were collected.
Results In all, 964 patients were included, mostly <65 years old (75 %) and classified as being overweight (68 %). Disease was diagnosed as being up to stage IIA in 54.9 % of the cases; 65.1% underwent mastectomy and 83.8% had total axillary dissection. As adjuvant treatment, 61 % underwent chemotherapy, 63.5 % radiotherapy and 68 % hormone therapy. Among surgical complications, 62.6 % of patients had seroma, 40.7 % had necrosis, 35.9 % axillary web syndrome and 31.4 % lymphoedema. There was no association between axillary web syndrome and the development of lymphoedema (OR = 0.87, 95 % CI 0.65 to 1.15, $p = 0.329$).
Conclusion The occurrence of axillary web syndrome was not a risk factor for lymphoedema after 10 years of follow-up.

Keywords Axillary web syndrome · Lymphoedema · Breast cancer · Treatment

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Introduction

According to estimates from the National Cancer Institute for the biennium 2016/2017, 57,960 new cases of breast cancer are expected to be diagnosed in Brazil. Excluding non-melanoma skin cancers, this is the most common among women in almost all regions of the country [1]. If diagnosed and treated at an early stage, the disease has a good prognosis. However, in Brazil, this diagnosis is still performed at a late and more advanced stage, resulting in the need to perform more aggressive treatments [2, 3]. Surgery is the main treatment and is usually accompanied by an axillary approach, through sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) [4].

Axillary approaches provide essential information for the proper staging of breast tumours and therapeutic decision-making, but bring with it some types of postoperative morbidity, such as pain, paraesthesia, lymphoedema, decreased range of motion and strength in the upper limb, axillary web syndrome (AWS), postoperative infection and seroma, affecting the involved upper limb functionality and, consequently, the ability to perform daily living activities [5]. Among complications arising from treatment, lymphoedema is one of the most important, due to its chronic and disabling condition,

leading to a predisposition to infections and generating important physical, social and psychological problems [6].

Lymphoedema is defined as an abnormal, widespread or regional accumulation of interstitial fluid, rich in proteins, resulting in the formation of oedema, and possibly in chronic inflammation with or without fibrosis. It occurs mainly as the result of malformation, underdevelopment or acquired disruption of lymphatic circulation. This failure is usually classified as primary or acquired (secondary) and as acute or chronic. In breast cancer patients, lymphoedema is acquired as a result of the removal of axillary lymph nodes and lymphatic vessels as a therapeutic intervention [7, 8]. In the literature, several factors are associated with the occurrence of lymphoedema, for example, the type of treatment received (increased risk for women undergoing mastectomy, axillary lymph node dissection), socio-demographic characteristics and lifestyle, such as obesity, age and postoperative complications [8].

Another postoperative complication is AWS, which is characterised by the appearance of fibrous cording and is visible and palpable under the skin of the axilla and in the medial arm toward the elbow region, appearing between 5 and 8 weeks after surgery. It is a self-limiting process because the cords can cause axillary pain radiating to the ipsilateral arm, restriction in range of motion, numbness and tightness, functional impairment to the shoulder joint and even delays in the start of radiotherapy (due to limited range of motion). The complication is not accompanied by fever or redness. In the literature, the incidence ranges from 20 % after SLNB to between 38 and 72 % after ALND. The condition usually resolves spontaneously within 3 months [9–11].

The AWS pathophysiology is not fully understood, but hypotheses posit discontinuation of axillary lymphatics as the factor that creates the syndrome [12]. Moskovitz et al. suggested that the removal of axillary lymph nodes could promote AWS through three mechanisms: the lymphovenous damage due to tissue retraction and positioning of the patient during lymph node dissection, the release of tissue factors that may cause hypercoagulability in the surrounding tissues and stasis in venous and lymphatic channels induced by removal of axillary lymph vessels that drain the arm [13].

In the literature, there are still no treatment guidelines set for AWS. The main treatments described are home exercises with gentle movements, pendular shoulder movement, walking fingers on the wall, active and passive stretching and manual traction. However, such treatments are carried out according to professional experience since there are no studies in the literature demonstrating the benefits of each technique [12, 14–17].

Although AWS is identified as a risk factor for lymphoedema through consensus among professionals working in the field, available literature is still not clear about the relationship among these characteristics. The hypothesis that the AWS is a risk factor for lymphoedema arises from a thought where possible pathophysiology of these two complications is related [18]. This study aims to evaluate the association between axillary web syndrome and the development of lymphoedema after 10 years of follow-up.

Material and methods

This is a prospective cohort study in women with breast cancer diagnosed and treated at a public referral centre for cancer. Women were included if they had a diagnosis of breast cancer and received breast-conserving surgery or mastectomy associated with axillary lymph node dissection (stages I, II or III) between August 1, 2001 and November 30, 2002. Patients who underwent cancer treatment at another institution had previous contralateral breast cancer or synchronous bilateral breast cancer, were diagnosed with lymphoedema or functional changes at any of the upper limbs prior to the surgical treatment, underwent palliative surgery with the presence of distant metastasis or were not able to answer the questions were excluded.

Patients were followed according to the physical therapy service routine described in Bergmann et al. [14] before and after surgery, 30 days, 6 months and annually until 5 years after surgery. Patients who developed physical and functional changes identified were referred to treatment groups. Between periods of follow-up, patients in need of physiotherapy care were instructed to make an appointment with physical therapy.

A review of the medical records was conducted, and women without a lymphoedema diagnosis during the follow-up and those with lack of disease progression and those that received a physical therapy evaluation prior to the follow-up period were requested to attend an assessment 10 years post-surgery.

Axillary web syndrome was characterised by the presence of a palpable lymph fibrous cord in the upper limb and/or ipsilateral axillary surgery, which may or may not be associated or with pain and joint restriction of the arm. Lymphoedema was measured over the circumference of the upper limbs, with measurements made 7 and 14 cm above and 7, 14 and 21 cm below the elbow articular line. The segment volume was calculated by the following: $V = h * (C^2 + Cc + c^2) / (p * 12)$, where V is the volume of the segment member, C and c are the circumference between points and h is the distance between the circumferences (C and c). The sum of the difference between each point corresponds to the estimated final volume. The volume of the limbs was compared and was considered as lymphoedema if there was a difference between the limbs of >200 ml.

In order to describe the population, socio-demographic, clinical and tumour characteristics were collected (Table 1). The CEP/INCA approved this study under the 42/02 number, and an addendum to this project was carried out to increase the initial follow-up of 2 to 10 years with approval dated January 26, 2012.

A descriptive analysis was performed using measures of central tendency and dispersion for continuous variables and relative and absolute frequency for categorical variables. To

Table 1 Independent variables

Independent variables	Stratification
Age of the patient	<65 years ≥65 years
Marital status	With partner (married and non-formal unions) Without a partner (single, widowed, separated)
Educational level	Incomplete basic education Secondary/higher
Occupation	Housewife Others
Body mass index (BMI)	Underweight (BMI < 18.5) Suitable (BMI ≥ 18.5 to <25.0) Overweight (BMI ≥ 25.0)
Axillary lymph node dissection	Total Partial
Radiotherapy	Neoadjuvant Adjuvant
Hormone therapy	Neoadjuvant Adjuvant
Chemotherapy	Adjuvant Neoadjuvant
Number of positive lymph nodes	>4 <4
Tumour staging	Initial staging (until IIA) Late stage (>IIB)
Surgery	Mastectomy Conservative
Breast reconstruction	Immediate Late
Cicatricial complications	Seroma Necrosis Dehiscence Among others

evaluate the association between AWS and lymphoedema, a univariate logistic regression was performed using odds ratios and their respective confidence interval of 95 %.

Results

In the present study, 964 patients were included, with a mean age of 55 years (SD ± 12.98). Regarding the socio-demographic profile, most patients had a partner (52.1 %), incomplete basic education (51.9 %) and performed exclusively home activities (61.2 %). Regarding nutritional status, 30.0 % had weight in the suitable range, while 68.3 % were overweight (Table 2).

Characteristics of the treatment and the histopathological examination are described in Table 3. Regarding the oncological therapy, most patients underwent mastectomy (65.1 %) and total axillary dissection (83.8 %). The mammary reconstruction was performed immediately in 5.5 % of cases and belatedly in 6.7 % of cases. Considering the histopathological stage of breast cancer, most patients were classified as stage IIA (54.9 %) or earlier and had less than four positive lymph nodes (82.0 %). As neoadjuvant treatment, chemotherapy was performed in 22.1 % of cases, radiotherapy in 1.8 % and hormonotherapy in 2.1 % of cases. Regarding the adjuvant treatment, chemotherapy was performed in 61.0 % of cases, radiotherapy in 63.5 % and hormone therapy in 68.0 % of cases.

Table 2 Socio-demographic characteristics at the time of surgery ($n = 964$)

Variables	N (%)[a]
Age group	
<65 years	723 (75.0)
≥65 years	241 (25.0)
Marital status	
With partner	457 (47.9)
Without a partner	497(52.1)
Educational level	
Incomplete basic education	480 (51.9)
Secondary/higher	445(48.1)
Profession	
Housewife	450 (61.2)
Others	285 (38.8)
Nutritional status	
Underweight	16 (1.7)
Suitable	289 (30.0)
Overweight	659 (68.3)

[a] Differences in sample size correspond to the absence of information

Among the surgical complications, 62.6 % of patients presented seroma and 40.7 % had necrosis. A lower proportion axillary web syndrome (35.9 %), lymphoedema (31.4 %) and wound infection (12.9 %) was observed. Regarding the evaluation of the association between axillary web syndrome and the development of lymphoedema in 10 years of follow-up, statistical significance was not observed (OR = 0.87, 95 % CI 0.65 to 1.15, $p = 0.329$) (Tables 4).

Discussion

The study population was predominantly made up of women, with an average age of 55 years at the time of surgery and who were overweight. These findings are consistent with the findings of Brito [19], the American Cancer Society [20] and Wang et al. [21]. Ageing is the main risk factor for the development of breast cancer, given the accumulated exposures of risk factors and hormonal changes of age that favour the emergence of this cancer [20, 21]. Excess body weight is also an important risk factor associated with an increased risk of

Table 3 Characteristics of the treatment and histopathologic exam

Variables	*N* (%)[a]
Surgery	
Mastectomy	622 (65.1)
Conservative	334 (34.9)
Immediate reconstruction	
Yes	53 (5.5)
No	906 (94.5)
Late reconstruction	
Yes	65 (6.7)
No	899 (93.3)
Neoadjuvant chemotherapy	
Yes	213 (22.1)
No	751 (77.9)
Adjuvant chemotherapy	
Yes	587 (61.0)
No	376 (39.0)
Axillary lymph node dissection level	
Total	764 (83.8)
Partial	148 (16.2)
Staging	
Until IIA	525 (54.9)
≥IIb	432 (45.1)
Positive lymph nodes	
>4	174 (18.0)
<4	790 (82.0)
Adjuvant radiotherapy	
Yes	612 (63.5)
No	352 (36.5)
Neoadjuvant radiotherapy	
Yes	17 (1.8)
No	946 (98.2)
Neoadjuvant hormone therapy	
Yes	20 (2.1)
No	944 (97.9)
Adjuvant hormone therapy	
Yes	656 (68,0)
No	308 (32,0)

[a] Differences in sample size correspond to missing information

Table 4 Post-surgical complications in the ipsilateral upper limb

Variables	*N* (%)[a]
Axillary web syndrome	
Yes	346 (35.9)
No	618 (64.1)
Lymphoedema	
Yes	303 (31.4)
No	661 (68.6)
Seroma	
Yes	575 (62.6)
No	344 (37.4)
Wound infection	
Yes	119 (12.9)
No	801 (87.1)
Necrosis	
Yes	374 (40.7)
No	546 (59.3)

[a] Differences in sample size correspond to the absence of information

mortality, which was 1.5 times higher in women who were overweight and about two times higher in obese compared to in lean women [20].

Out of the 964 participants evaluated, 54.9 % were classified as being at or before stage IIA and 82 % had less than four positive lymph nodes, indicating less advanced degree of staging than expected in the literature [3, 22–25]. Dugno et al. [24] also found, in a study of 273 patients of the southern region of Brazil, a greater incidence of initial staging (staging I and II, 36.6 and 34.2 %, respectively). However, in Abraham et al. [3] study, conducted with 59,317 women from all parts of Brazil, 53.5 % of participants had advanced stage (>IIB), a finding also found in Soares et al. [26] study, which noted higher percentage of women with stage III or IV cancer. These advanced cancer stages are seen more often in the public service compared to in the private.

Concerning oncological therapy, most patients underwent mastectomy (65.1 %) and total axillary dissection (83.8 %). These numbers are larger than those found by the American Cancer Society [20], where 58 % of women diagnosed between stages I and II underwent conservative surgery and 36 % underwent mastectomies, while for stages III and IV, 14 % underwent conservative surgery and 58 % underwent mastectomy. Simon et al. [22] compared treatment between public and private hospitals in Brazilian medical centres and identified an incidence of conservative surgery of 40.9 % in public and 51.7 % in private hospitals. It is suggested that in this study, the mastectomy frequencies are higher due to the size of the tumour, the surgical margin or the fear of recurrence, which are factors the American Cancer Society also described [20].

Still, in Simon et al. [22] study, neoadjuvant chemotherapy was performed in 26.5 % of patients in public hospitals, which is similar to that found in this study (22.1 %). Regarding adjuvant treatment, chemotherapy was performed in 61 % of the cases, radiotherapy in 63.5 % and hormone therapy in 68 % of case; however, data from Simon et al. [22] study of 4912 patients found that of those patients that were at a more advanced stage (III and IV), 88.4 % underwent chemotherapy, while 76 % underwent radiotherapy and 86.6 % hormone. It is possible that the frequencies found by Simon et al. [22] are greater than those in this study due to the advanced stage, which requires more aggressive treatment.

In the cohort of 964 participants of this study, an incidence of AWS of 35.9 % was identified, while for lymphoedema, it was by 31.4 %. There is a wide range of variation in the incidence of AWS and lymphoedema in the literature, depending on the conducted study design, diagnostic methodology and sample survey number. For AWS, the incidence ranges from 0.6 to 85 %, with the lowest observed in a study of 196 patients and the greater found in a study of 123 patients who underwent some kind of mammary surgery and had some type of symptom related to the syndrome [16, 23]. To date, we have found no studies with the same follow-up period.

Disipio et al. [27] performed a systematic review to identify the incidence of lymphoedema, and considering studies with prospective cohorts, the estimate found was 21.4 %, which was 10 % lower than that seen in this study. Still, according to this review, almost one in five women in North America, Australia, Asia and the Middle East with breast cancer develop lymphoedema secondary to the treatment, while in Europe, the UK and South America, less than one in six women develop this complication. Such differences may be related to several risk factors for developing lymphoedema, such as in North America, where sedentary lifestyles and obesity are prevalent among the population, favouring the appearance of this complication [20]. Lack of registration and information can also be associated with the lower incidence of lymphoedema found.

AWS was not statistically found to be a risk factor for lymphoedema in 10 years of follow-up. This result was in contrast to the results of Paiva et al. [28] study, as well as with the Practice Guidelines for Management of Lymphoedema [18], which describes the syndrome as a risk factor. The first study evaluated 250 women who underwent breast surgery at a hospital in Minas Gerais. Of these, 112 had lymphoedema, and within that group, 71 patients had AWS. In the comparison group, only 53 had the syndrome, showing statistical significance for the association of complications ($p < 0.01$) [28]. Regarding the second, the AWS was identified as a risk factor for lymphoedema through consensus among professionals working in the field [18]. Bergmann et al. [23] corroborated the findings of this study in which the frequency of early onset of oedema was not associated with AWS. Paiva et al. [29] also did not identify statistical significance between these two complications following model adjustment.

The hypothesis that AWS would be a risk factor for lymphoedema arises from a thought where possible pathophysiology of these two complications is related. Although not completely understood, the AWS pathophysiology is presupposed by the discontinuation of axillary lymphatics through three mechanisms: lymphovenous injury due to tissue retraction and positioning of the patient during lymphadenectomy, the release of tissue factors that may cause hypercoagulability in the surrounding tissues and by stasis of lymphovenous channels from output obstruction, induced by removal of axillary lymphatics that drain the arm, as well as lymphoedema, where the pathophysiology is described by the interruption of the lymphatic system (for example, caused by lymph node dissection, radiotherapy or tumour compression), leading to decreased lymph flow. Consequently, there is an increased hydrostatic pressure, causing congestion and progressive dilatation of lymphatics, thereby generating the accumulation of lymph in the affected upper limb [8, 13].

The presence of compensatory mechanisms, such as increased flow capacity of the lymph through collateral pathways or lymphatic regeneration can explain the reasons for not detecting lymphoedema in certain patients. Koehler [17] proposed one hypothesis for the lack of association between AWS and lymphoedema, which assumes that there might be a lymph mechanism that occurs during the development of the axillary cord, such as lymphatic regeneration with reconnection to existing lymphatic vessels, adhering to the underlying tissues. In a systematic review of AWS, Yeung, McPhail and Kuys [15] suggested that spontaneous resolution of the syndrome is associated with successful restoration of lymphovenous flow and/or gradual elimination of lymphatic vessels without function, while no resolution was related to incomplete reconnection. Koehler [17] also speculated that the treatment of AWS may have an increasing effect on the impact of the later development of lymphoedema, possibly by breaking newly formed lymphatic vessels in the healing phase. Different treatments have been proposed for AWS, such as active exercises, stretching, massage and manual traction, but the actual effect of these treatments is not known for lymphatic vessels, as the AWS pathophysiology is not completely known and such treatments are performed according to the experience of each professional [12, 14–17].

Manual traction, which is performed routinely for the treatment of AWS, combined with other techniques, as outlined by the National Cancer Institute (INCA), consists of gentle passive stretching of the fibrous cord until there is a release, which provides gain in the range of motion immediately after an audible click, with patients reporting mild pain only at the time of disruption and no other negative effects associated [14, 15]. Several studies [15–17] express concern with the performance of this technique and suggest switching to softer and less aggressive techniques due to a lack of knowledge about the aetiology and pathophysiology of the syndrome.

Cho et al. [11] evaluated the effects of physiotherapy associated with manual lymphatic drainage in 41 patients with AWS, observe increased strength, improved range of motion and pain reduction. Manual lymphatic drainage was effective in reducing pain and arm volume in patients whit AWS who developed lymphoedema.

It can be assumed, due to the results of the present study, that the treatment performed for the AWS does not have an impact on the development of lymphoedema, since all of the participants in this study underwent the same treatment, and after 10 years of follow-up, there was no statistical

significance between axillary web syndrome and the development of lymphoedema. These findings are reinforced by the study of Cho et al. [11], where physical therapy restored shoulder ROM and improved muscular strength in all patients, reasserting that physical therapy is a quick and effective method to prevent and recover shoulder disorder.

Conclusion

Axillary web syndrome was not significantly associated with lymphoedema in women undergoing surgery for breast cancer after 10 years of follow-up.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest. We have full control of all primary data and we agree to allow the journal to review their data if requested.

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