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Risk Factors for Arm Lymphedema in a Cohort of Breast Cancer Patients Followed up for 10 Years

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Keywords

Breast cancer · Lymph node dissection · Radiotherapy · Risk factors · Lymphedema

Summary

Background: The etiology of lymphedema is multifactorial, and definition criteria of lymphedema, its limitation, and follow-up must be considered in studies related to risk factors. The aim of this study is to evaluate risk factors related to arm lymphedema in a cohort study with a long follow-up. **Patients and Methods:** The study was performed in 622 breast cancer patients. The main endpoint reported was the presence of clinical lymphedema reported in medical records. Univariate and multivariate regression analyses were performed to identify factors related to lymphedema. **Results:** 66.4% of the patients were submitted to mastectomy, 88.4% to level III axillary lymphadenectomy, 34.9% to radiotherapy in the supraclavicular fossa, and 4.3% to axillary radiotherapy. The mean follow-up was 96.7 months. 45 patients (7.2%) developed lymphedema, of which 82.2% had developed lymphedema at 60 months. Univariate regression analysis showed that supraclavicular radiotherapy, adjuvant/palliative chemotherapy, ≥ 15 lymph nodes dissected, and axillary surgery increase the lymphedema rate by 1.87, 2.28, 2.03, and 6.17, respectively. Adjusted multivariate regression analysis showed that the combination of axillary dissection and number of lymph nodes dissected was the main factor related to lymphedema ($p = 0.017$). **Conclusion:** In the presentinel era, axillary dissection and the number of lymph nodes resected are related to 10-year lymphedema.

Introduction

Over 1.7 million new cases of breast cancer are estimated to occur each year. One-half of the new cases occur in developed countries, and 38% of the deaths [1]. The prognosis of breast cancer is good. The survival rate is 73% in developed countries and 57% in developing countries [2], a fact that reflects the growing number of breast cancer survivals.

The treatment of breast cancer has changed radically over the last 30 years, with an increase in conservative treatments and survival rates. In the 1980s, Veronesi et al. [3] and Fisher et al. [4] showed that the safety of conservative breast cancer treatments, without changing the patient's prognosis, was maintained even after a 20-year follow-up. Likewise, the sentinel lymph node has been used in breast cancer treatments and proven effective [5], thereby reducing the number of lymphadenectomies and their associated complications. However, axillary lymphadenectomy has an established role in the treatment of breast cancer and plays an important role in locoregional treatment. This treatment continues to be performed in developing countries, as breast cancer is diagnosed at advanced stages [6].

Because treatment modalities are associated with survival rate increases, their applications increase the incidence of sequelae. Thus, quality-of-life improvement and physiotherapy measures should be implemented to reduce or minimize these locoregional sequelae [7, 8]. Locoregional treatment measures can cause paresthesia, paresis, changes in shoulder mobility, and lymphedema [8, 9]. Upper-limb lymphedema is a chronic disabling sequel caused by lymphatic insufficiency; its prevalence varies from 6% to 49% among patients undergoing lymphadenectomies, and its incidence ranges from 0% to 22% [7, 9, 10]. The methods used for diagnosis, survival rate assessment, and patient follow-up influence the inci-

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Table 1. Univariate analysis (χ^2) of clinical and sociodemographic variables related to lymphedema

Variable	Category	Lymphedema		Total	p
		Absent	Present		
Age	40–69	456 (93.3%)	33 (6.7%)	489	0.45
	> 70 years old	121 (91.0%)	12 (9.0%)	133	
Schooling	illiterate	452 (93.4%)	32 (6.6%)	484	0.23
	1st/2nd degree	87 (88.8%)	11 (11.2%)	98	
	tertiary degree	38 (95.0%)	2 (5.0%)	40	
BMI	< 30	352 (93.6%)	24 (6.4%)	376	0.47
	≥ 30	139 (91.4%)	13 (8.6%)	152	
Clinical stage[a]	0 + I	123 (92.5%)	10 (7.5%)	133	0.72
	II	227 (93.4%)	16 (6.6%)	243	
	III	203 (91.4%)	19 (8.2%)	222	
TNM-T	Tis	40 (95.2%)	2 (4.8%)	42	0.08
	T1	121 (88.3%)	16 (11.7%)	137	
	T2	278 (93.3%)	20 (6.7%)	298	
	T3	38 (100%)	0	38	
	T4	74 (91.4%)	7 (8.6%)	81	
	Tx	26 (100)	0	26	
TNM-N	N0	285 (93.4%)	20 (6.6%)	305	0.77
	N1	127 (92.7%)	10 (7.3%)	137	
	N2	63 (91.3%)	6 (8.7%)	69	
	N3	74 (90.2%)	8 (9.8%)	82	
	Nx	28 (96.5%)	1 (7.2%)	29	
TNM-M	M0	577 (92.8%)	45 (7.2%)	622	–

BMI = Body mass index, M0 = TNM absence of metastasis.
[a]Cases with missing values were removed from the analysis.

dence of lymphedema, and this fact is reflected in the evaluation of factors related to the occurrence of this condition [7, 10]. In this new era of breast cancer, survival is evaluated after 10 years. The following factors are related to lymphedema: axillary lymphadenectomy, radiotherapy, mastectomy, the presence of positive lymph nodes, higher body mass index, trauma, and infection in the arm [7, 10]. Changes in the definition of lymphedema, based on different methods, cut-off values and follow-up might influence the findings [11]. Few studies have evaluated the factors related to lymphedema among patients monitored over 10 years. Moreover, most publications examine a limited number of patients, and the diagnostic methodologies are diverse. These facts motivated the present study.

Patients and Methods

This retrospective study was conducted at a tertiary oncology hospital using the medical records of women with breast cancer diagnosed from 1998 to 2001. We sought to evaluate the tumor characteristics at diagnosis, the type of treatment conducted, and the survival rate as well as its relationship with the presence of clinical lymphedema. Patients who underwent a previous treatment at another institution or who were metastatic at diagnosis, less than 40 years of age or male were excluded. Data collection was performed using a standardized form.

Tumors smaller than 3 cm were the standard indication for quadrantectomy during the study period. Level III axillary lymphadenectomy was the standard treatment used to treat the axilla. Breast reconstruction was delayed in most cases. Hormone therapy was applied in patients who were estrogen receptor positive. Neoadjuvant chemotherapy was often used for patients with stage III tumors. Adjuvant radiotherapy on the chest wall was used in quadrantectomies. The use of radiotherapy for mastectomies occurred primarily in patients with tumors larger than 5 cm, skin infiltration, grade III tumors, inadequate axillary dissection (< 10 nodes), extracapsular invasion, compromised margins (< 1 cm), or 4 or more lymph nodes. Preferably, radiotherapy was not performed on the axilla of patients who underwent axillary lymphadenectomies. Radiotherapy was conducted on the supraclavicular fossa (SCF) of patients with 4 or more axillary lymph nodes.

Patients with lymphedema at the first date described in the medical records were considered, regardless of improvement after physical therapy. We used the standardized tumor/node/metastasis (TNM) rating system (6th edition). Data from this standardized form were analyzed using IMB® SPSS® Statistics, version 20.0.

Data analysis began with obtaining the simple frequency of the variables. In this regard, the frequency of lymphedema and its appearance since treatment start was evaluated. We dichotomized these findings to identify the factors related to the onset of lymphedema. To this end, the categorical variables were analyzed using the chi-square test, and only 2 characteristics were analyzed (simple analysis). Later, a multiple logistic regression was used to assess the combined relationship of the characteristics related to the presence of lymphedema. The significant variables comprised less than 10% of those selected for the multivariate analysis. Overall survival (OS) time (i.e., death for any reason), cancer-specific survival time (i.e., deaths due to cancer), and survival time until the occurrence of lymphedema were estimated using the nonparametric Kaplan-Meier method and by comparing the curves using the log-rank test. Probability values less than 5% were considered significant.

Results

From 1998 to 2001, 1,011 patients were treated; however, applying the exclusion criteria, only 622 patients were selected for this study. The mean age was 58.7 years (range = 40–95.5 years), and 77.5% of the patients were 40–69 years old. The patient and tumor

Table 2. Univariate analysis (χ^2) of treatment variables related to lymphedema

Variable	Category	Lymphedema		Total	p
		Absent	Present		
Type of mammary surgery	biopsy	38 (97.4%)	1 (2.6%)	39	0.41
	quadrantectomy	159 (93.5%)	11 (6.5%)	170	
	mastectomy	380 (92.0%)	33 (8.0%)	413	
Axillary surgery	absent	71 (98.6%)	1 (1.4%)	72	0.02
	present	506 (92.0%)	44 (8.0%)	550	
Lymph nodes dissected	absent	71 (98.6%)	1 (1.4%)	72	0.01
	1–14	189 (95.0%)	10 (5.0%)	199	
	≥ 15	316 (90.3%)	34 (9.7%)	350	
Lymph nodes involved[a]	absent	245 (92.5%)	20 (7.5%)	265	0.79
	1–9	187 (92.1%)	16 (7.9%)	203	
	≥ 10	73 (90.1%)	8 (9.9%)	81	
Breast reconstruction[a]	absent	483 (92.7%)	38 (7.3%)	521	0.77
	present	82 (94.3%)	5 (5.7)	87	
Neoadjuvant chemotherapy	absent	480 (93.2%)	35 (6.8%)	515	0.35
	present	97 (90.7%)	10 (9.3%)	107	
Neoadjuvant radiotherapy	absent	565 (92.8%)	44 (7.2%)	609	1.00
	present	12 (92.3%)	1 (7.7%)	13	
Adjuvant chemotherapy	absent	128 (93.4%)	9 (6.6%)	137	0.07
	ADJ	374 (94.0%)	24 (6.0%)	398	
	ADJ + PAL/PAL	75 (86.2%)	12 (13.8%)	87	
Breast adjuvant radiotherapy	absent	11 (91.7%)	1 (8.3%)	12	0.60
	present	566 (92.8%)	44 (7.2%)	610	
Supraclavicular radiotherapy	absent	382 (94.3%)	23 (5.7%)	405	0.05
	present	195 (89.9%)	22 (10.1%)	217	
Axillary adjuvant radiotherapy	absent	551 (92.6%)	44 (7.4%)	595	0.71
	present	26 (96.3%)	1 (3.7%)	27	
Hormone therapy	absent	304 (93.3%)	22 (6.7%)	326	0.64
	ADJ + PAL	273 (92.2%)	23 (7.8%)	296	
Patient status	cancer death	158 (95.2%)	8 (4.8%)	166	0.27
	non-cancer death	40 (90.5%)	4 (9.1%)	44	
	alive without cancer	318 (92.7%)	25 (7.3%)	343	
	alive with cancer	43 (92.8%)	7 (14.0%)	50	
Total (M0)	M0	577 (92.8%)	45 (7.2%)	622	–

ADJ = Adjuvant, PAL = palliative.
[a]Cases with missing values were excluded from the analysis.

characteristics are reported in table 1. With regard to treatment, 66.4% of the patients underwent mastectomies; 88.4% underwent axillary lymphadenectomies, 56.3% of which had more than 15 lymph nodes dissected. Adjuvant radiotherapies of the chest wall, the SCF, and the axilla were conducted in 98.1%, 34.9%, and 4.3% of the patients, respectively. The patient treatments are reported in table 2.

The mean follow-up period was 77.6 months (median = 85.3 months, range = 1.84–290.2 months). After excluding those patients who died, however, the mean follow-up period was 96.7 months (median = 93.6 months, range = 3.1–290.2 months), and only 8.7% of the patients had a follow-up period of less than 60 months). The attrition rates at the 60- and 120-month follow-up assessments were 1.3% and 4.0%, respectively. At the end of the study, 26.7% of the patients had died due to cancer, and 7.1% of the patients had died due to other causes. A total of 8.0% of the patients showed recurrence, and 55.2% lived without evidence of the disease. The cancer-specific survival rates at 5 and 10 years were 78.9% and 68.2%, respectively, and the OS rates at 5 and 10 years were 74.6 and 61.0%, respectively (fig. 1).

The overall rate of lymphedema was 7.2%. The mean time for lymphedema development was 25.5 months (median = 38.1 months, range = 1.5–114.2 months). Patients with lymphedema had longer mean follow-up times (95.7 × 76.1 months, p = 0.002) and better survival rates (p = 0.08; fig. 2a). Of the 45 patients with lymphedema, the cumulative percentages of this disease at 24, 36, 60, and 120 months were 46.7%, 57.8%, 82.2%, and 100%, respectively (fig. 2b). The simple analysis (χ^2) revealed that none of the sociodemographic or clinical variables was related to lymphedema (table 1). When evaluating the treatments, however, axillary surgery (p = 0.02) and SCF radiotherapy (p = 0.05) were related to lymphedema (table 2). The simple logistic regression model evaluated the following variables: SCF radiotherapy (p = 0.04), chemotherapy type (p = 0.05), lymphadenectomy/number of dissected

lymph nodes (p = 0.02), and axillary surgery (p = 0.07). The adjusted logistic regression analysis showed that lymphadenectomy/number of dissected lymph nodes was independently related to the onset of lymphedema (p = 0.02; table 3).

Discussion

The current new era of breast cancer treatment is marked by fewer breast and axillary surgeries and improved radiotherapy, leading to decreased treatment sequelae. Numerous patients in Brazil are diagnosed at an advanced stage; therefore, mastectomies and axillary lymphadenectomies remain the most frequently used treatments. However, this improved therapeutic arsenal has not only increased the survival rates and the numbers of survivors but it has also increased the number of sequelae related to breast cancer. The most frequent of these is lymphedema, which has a variable incidence based on the frequency of follow-up and the evaluation method employed [9].

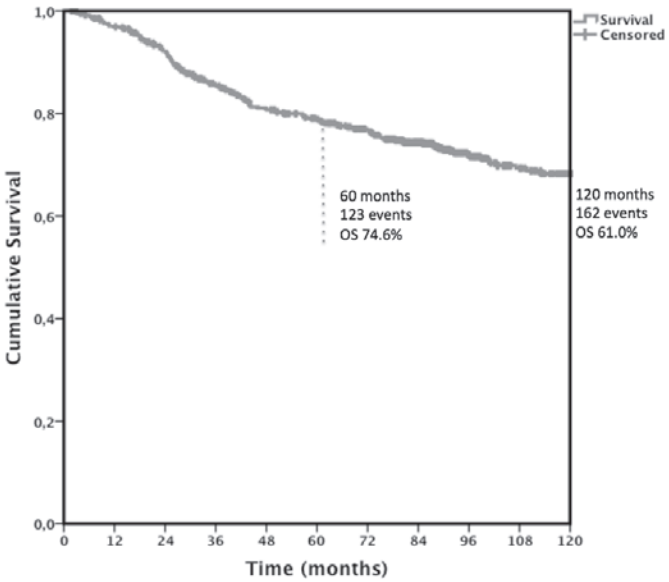

Fig. 1. Kaplan-Meier OS. C = Censure.

Patients often complain of swollen arms, weight gain, and difficulty moving; however, 18% of patients with lymphedema are asymptomatic [12]. The diagnosis is clinical and can be completed via perimetric or volumetric assessment of the arm. The most accurate clinical method is volumetry using the displacement of water (i.e., the Archimedes principle); a difference of 10% or 200 ml is diagnosed as lymphedema. However, the cone (i.e., frustum) calculation can also be used, which assesses the sum of the cones, using the perimeter and height or other geometric volumes (e.g., cylindrical and trapezoidal). This calculation has good reliability [7]. Positivity is superior when associated methods are applied [7]. Although volumetry is precise, this method is difficult to use, and perimetry is often used instead. Bioimpedance spectroscopy (BIS) increases the rate of lymphedema. It is an accurate method [13], but it is infrequently used in clinical practice, mainly, due to equipment costs.

When evaluating prospective studies that measure limbs, we must evaluate the methodology used to define lymphedema as well as the cut-off point that guides diagnosis and defines the treatment. In a prospective study of 1,253 patients, Blanchard et al. [14] made diagnoses based on the data obtained by using a questionnaire or a telephone interview. Ozcinar et al. [15] used a perimetric difference greater than 2 cm between the pre- and post-operative measures to diagnose lymphedema. In retrospective studies, the definition of lymphedema is usually examiner dependent. It depends on

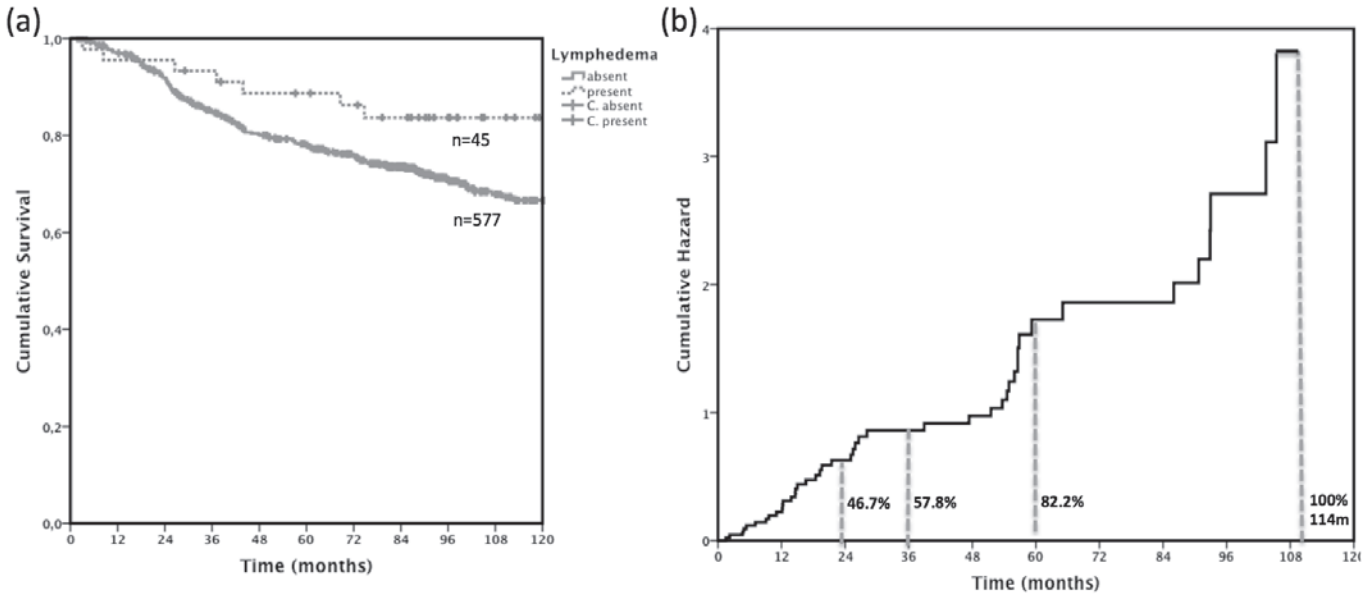

Fig. 2. Lymphedema and survival: **(a)** OS related to the absence or presence of lymphedema (p = 0.08); **(b)** cumulative hazard ratio related to the appearance of lymphedema during follow-up. C = Censure.

Table 3. Adjusted and non-adjusted logistic regression of factors related to lymphedema

Model	Variable	Category	Risk	CI (95%)	p
Non-adjusted	lymph nodes dissected	absent	1.00	–	0.021
		1–14	3.13	0.38–25.88	
		≥ 15	7.57	1.02–56.09	
	axillary surgery	absent	1.00	–	0.074
		present	6.17	0.84–45.51	
	adjuvant chemotherapy	absent	1.00	–	0.046
		ADJ	0.91	0.41–2.01	
		ADJ + PAL/PAL	2.28	0.92–5.65	
	SC adjuvant radiotherapy	absent	1.00	–	0.043
		present	1.87	1.02–3.45	
Adjusted	lymph nodes dissected	absent	1.00	–	0.017
		1–14	3.70	0.42–32.10	
		≥ 15	9.12	1.15–72.12	
	adjuvant chemotherapy	absent	1.00	–	0.051
		ADJ	0.50	0.21–1.17	
		ADJ + PAL/PAL	1.15	0.42–3.15	
	SC adjuvant radiotherapy	absent	1.00	–	0.177
		present	1.57	0.81–3.05	

CI = Confidence interval, ADJ = adjuvant, PAL = palliative, SC = supraclavicular.

the patients' complaints and the professional volumetric evaluation, regardless of the criteria used. Thus, the definition might be biased because it groups together symptomatic patients and those with larger-volume lymphedema. Bergmann et al. [16] analyzed the lymphedema diagnosis method used among 394 women and found a concordance of 81% between their medical record data and perimetry. This finding demonstrates a good specificity of the method used in our study because we applied data from medical records.

The follow-up time can also influence the rate of lymphedema. Armer and Stewart [11] prospectively evaluated 236 patients using different methods for the lymphedema definition. A Kaplan-Meier curve was created with the patients, reported as lymphedema disease-specific survival. They observed that the incidence increased during follow-up and depending on the diagnosis method: At 60 months, the disease-specific survival was 43% for patient reports of limb heaviness and swelling, 55% for a 10% difference in perimetric limb volume change, 83% for a 200-ml perimetric limb volume change, and 94% for a 2-cm circumferential change. Petrek et al. [17] evaluated patients who had survived 20 years after their treatment began. Specifically, they evaluated 263 patients from a cohort of 923 patients. The authors noted a lymphedema rate of 13%, with lymphedema defined as a difference of 2 cm in circumference. A total of 77% of patients with lymphedema were diagnosed in the first 3 years, with an annual increase of 1% per year. Our study was one of the largest series of patients followed up for a long period [7] as we sampled a cohort of 622 patients with a median follow-up time of 96.7 months, and only 4% of the patients were lost to follow-up. The lymphedema rate was 7.2% (45/633) over time, and the cumulative distributions of the cases at 24, 36, 60, and 120 months were 46.7%, 57.8%, 82.2%, and 100%, respectively. Thus, 60 months was a sufficient amount of time to diagnose 82.2% of patients, and it was the minimum time to be considered in studies on this topic. The use of palliative chemotherapy was another factor in this series. This therapy was applied in patients with recurrent and metastatic disease, whose risk was increased 2.28 times. This finding also explains the need for longer follow-up periods.

Some patients passed away due to breast cancer (i.e., those with risk factors), thereby reducing the incidence of lymphedema. We observed that patients with lymphedema had a better survival rate, although this difference was not significant. This finding should be interpreted such that patients with lymphedema represent a group of survivors, and therefore a selection bias exists. Lymphedema is predominantly a delayed complication in the surgical treatment of cancer, which reinforces the need for studies that relate the risk factors for lymphedema to long-term follow-up assessment and the necessity to include numerous patients, as was the case in the current study.

Lymphedema is related to surgical techniques and systemic treatments that (either alone or together) increase its incidence. A great deal of evidence shows that extensive surgery (e.g., axillary lymphadenectomies, numerous dissected lymph nodes, and mastectomies) has strong effects in this regard [7]. In a retrospective study of 400 patients followed up at 4.7 years, Ververs et al. [18] observed a 9% lymphedema rate. Furthermore, the risk of lymphedema was 3.57 times higher among patients who underwent radiotherapy of the axilla and SCF compared with non-irradiated patients and those subjected to axillary lymphadenectomies. In a prospective study, Ozcinar et al. [15] observed, after a 5-year follow-up, that radiotherapy was associated with an increased risk of lymphedema. This finding reinforces the validity of studies with longer follow-up periods. Bergmann et al. [19] observed that radiotherapy increased the risk of lymphedema 4.44 times. 2 aspects should be considered with regard to the patients of the current

study who underwent axillary lymphadenectomies: Axillary radiotherapy was not performed, and SCF radiotherapy was associated with lymphedema risk only in the univariate analysis and was not significant in the multivariate analysis.

Previous studies have shown that the use of radiotherapy is directly related to the degree of regional lymph node involvement [20]. The risk of supraclavicular lymph node involvement is greater when 4 or more lymph nodes are positive for axillary dissection. In these cases, SCF radiotherapy is indicated because evidence exists that this method reduces the chance of nodal recurrence and progression to systemic disease and improves the effect on disease-free survival and OS rates [21]. SCF radiotherapy increased the rate of lymphedema by 1.87. Axillary lymphadenectomies alter the axillary lymphatic drainage, but the association between lymphadenectomy and SCF radiotherapy simultaneously worsens the lymphatic drainage. Furthermore, Hayes et al. [22] demonstrated that the most severe cases of lymphedema are more related to SCF radiotherapy.

A higher number of lymph nodes involved in lymphadenectomy increases the risk of lymphedema [7]; however, these studies were conducted in the pre-sentinel node era when numerous patients without metastatic disease in the axilla underwent lymphadenectomy (as in the present study). Nevertheless, this factor was not significant in the univariate analysis. Paiva et al. [23] found that the number of lymph nodes dissected, or the extent of axillary dissection, is directly linked to an increased risk of lymphedema. Our study has 2 important findings: Axillary lymphadenectomies increase the risk of lymphedema 6.17 times, and the dissection of more than 15 lymph nodes increased the risk of lymphedema 2.03 times. We must remember, however, that the number of lymph nodes found might be related to the surgical techniques, the level of lymphadenectomy, the pathologist, or to neoadjuvant chemotherapy. Moreover, with the increasing number of early detected tumors due to the improved structuring of the health network, the increase in the sentinel node indications and the results of the Z0011 study [24] have decreased the rate of axillary lymphadenectomies associated with rehabilitation and the need for physical activity [25]. This treatment will substantially reduce the lymphedema rates, which underlines the importance of the presentation of this series, in which numerous patients were assessed after a long period.

Disclosure Statement

None of the authors of this study have any financial or personal conflicts of interest to disclose.

References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
2 Parkin DM, Bray F, Ferlay J, Pisani P: Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
3 Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, Aguilar M, Marubini E: Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227–1232.
4 Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N: Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–1241.
5 Giuliano AE, Jones RC, Brennan M, Statman R: Sentinel lymphadenectomy in breast cancer. J Clin Oncol 1997;15:2345–2350.
6 Liedke PE, Finkelstein DM, Szymonifka J, Barrios CH, Chavarri-Guerra Y, Bines J, Vasconcelos C, Simon SD, Goss PE: Outcomes of breast cancer in Brazil related to health care coverage: a retrospective cohort study. Cancer Epidemiol Biomarkers Prev 2014;23:126–133.
7 DiSipio T, Rye S, Newman B, Hayes S: Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013;14:500–515.
8 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;31:302–309; quiz 310–301.
9 Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S, Hachey M, Kirch R, Jemal A, Ward E: Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012;62:220–241.
10 Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GK, Scott-Conner C: The risk of developing arm lymphedema among breast cancer survivors: a meta-analysis of treatment factors. Ann Surg Oncol 2009;16:1959–1972.
11 Armer JM, Stewart BR: Post-breast cancer lymphedema: incidence increases from 12 to 30 to 60 months. Lymphology 2010;43:118–127.
12 Fu MR, Axelrod D, Haber J: Breast-cancer-related lymphedema: information, symptoms, and risk-reduction behaviors. J Nurs Scholarsh 2008;40:341–348.
13 Warren AG, Janz BA, Slavin SA, Borud LJ: The use of bioimpedance analysis to evaluate lymphedema. Ann Plast Surg 2007;58:541–543.
14 Blanchard DK, Donohue JH, Reynolds C, Grant CS: Relapse and morbidity in patients undergoing sentinel lymph node biopsy alone or with axillary dissection for breast cancer. Arch Surg 2003;138:482–487; discussion 487–488.
15 Ozcinar B, Guler SA, Kocaman N, Ozkan M, Gulluoglu BM, Ozmen V: Breast cancer related lymphedema in patients with different loco-regional treatments. Breast 2012;21:361–365.
16 Bergmann A, Mattos IE, Koifman RJ: Diagnosis of lymphedema: analysis of the methods used in the evaluation of the upper limb in women undergoing axillary lymphadenectomy for breast cancer treatment. Rev Bras Cancerol 2004;50:311–320.
17 Petrek JA, Senie RT, Peters M, Rosen PP: Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. Cancer 2001;92:1368–1377.
18 Ververs JM, Roumen RM, Vingerhoets AJ, Vreugdenhil G, Coebergh JW, Crommelin MA, Luiten EJ, Repelaer van Driel OJ, Schijven M, Wissing JC, Voogd AC: Risk, severity and predictors of physical and psychological morbidity after axillary lymph node dissection for breast cancer. Eur J Cancer 2001;37:991–999.
19 Bergmann A, Koifman RJ, Koifman S, Ribeiro MJP, Mattos IE: Upper limb lymphedema following breast cancer surgery: prevalence associated factors. Lymphology 2007;40:96–106.
20 Falkson CB: How do I deal with the axilla in patients with a positive sentinel lymph node? Curr Treat Options Oncol 2011;12:389–402.
21 Xie L, Higginson DS, Marks LB: Elective regional nodal irradiation in patients with early-stage breast cancer. Semin Radiat Oncol 2011;21:66–78.
22 Hayes SB, Freedman GM, Li T, Anderson PR, Ross E: Does axillary boost increase lymphedema compared with supraclavicular radiation alone after breast conservation? Int J Radiat Oncol Biol Phys 2008;72:1449–1455.
23 Paiva DMF, Leite ICG, Rodrigues VO, Cesca MG: Associated factors of lymphedema in breast cancer patients. Rev Bras Ginecol Obstet 2011;33:75–80.
24 Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M: Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569–575.
25 Paskett ED, Dean JA, Oliveri JM, Harrop JP: Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. J Clin Oncol 2012;30:3726–3733.