ORIGINAL

Risk factors for development of upper limb lymphedema in patients submitted to surgery for breast cancer

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Abstract

Objective: Lymphedema (LE) is an important sequel of lymph node dissection for breast cancer. However, the etiology of LE has never been fully clarified, despite its negative impact on quality of life. The aim of this study was to identify risk factors for upper limb LE in patients submitted to surgery for breast cancer. **Methods:** This was a case-control study of 325 women with breast cancer submitted to axillary lymphadenectomy at the Ceará Cancer Institute between January 2000 and December 2007. The study population consisted of 101 LE patients and 224 controls. LE was defined as a ≥ 10% difference in volume between the upper limbs on plethysmography. The dependent variables included, age, body mass index, type of surgery, postoperative complications and type of adjuvant treatment. **Results:** The study identified three risk factors for LE: tumor stage II or higher (OR: 4.33; CI: 95%), surgical wound infection (OR: 1.0; CI: 95%) and irradiation of the supraclavicular fossa (OR: 2.90; CI: 95%). The prevalence of LE increased with the number of risk factors presented by each patient. The probability of developing LE was 6.95% for subjects with none of the risk factors identified in the study, 26.1% for one factor, 56% for two factors and 100% for all three factors. **Conclusion:** The main risk factors for LE identified in the present study were tumor stage II or higher, surgical wound infection and irradiation of the supraclavicular fossa. Based on these findings, an LE predictive score was devised for the study population.

Keywords: breast neoplasms, lymphedema, quality of life, risk factors, upper extremity.

INTRODUCTION

Lymph node involvement detected upon axillary lymphadenectomy is an important prognostic factor in patients with breast cancer (BC). However, lymphadenectomy causes a disruption of lymphatic vessels resulting in a functional overload of this system and consequently, accumulation of protein-rich fluid in the interstitial space[1,2]. This may contribute to the development of lymphedema (LE), although LE is known to be dependent on compensatory mechanisms of the lymphatic system and other factors as well. While many women show evidence of lymphedema, symptoms are temporary (up to 3 months) in about half the cases.[3] The incidence of LE ranges from 2-83%, with onset within six months of lymphadenectomy. Growing evidence suggest that most (70-80%) occurs up to 12 months after surgery for BC[3].

The large variation in published data is probably due to differences in diagnostic methods, which may be based on subjective criteria (clinical history and physical examination)[4-6] or objective criteria (manual perimetry, plethysmography, optoelectronic volumetry and bioimpedance)[7-9]. According to Kosir et al.[7] the diagnosis of upper limb LE requires a ≥ 10% difference in volume between the two limbs.

The objective of this study was to identify risk factors for the development of upper limb LE in women submitted to surgery for BC and to devise an LE predictive score.

METHODS

This was a case-control study involving 101 women referred to the Department of Physical Therapy of the Ceará Cancer Institute (ICC) between January 2000 and December 2007 with a clinical diagnosis of upper limb LE ≥ 18 months after surgery for BC. The control group consisted of 224 women submitted to surgery for BC without development of clinical LE. Patients with bilateral breast cancer, history of previous LE or orthopedic or rheumatic upper limb lesions were excluded from the study.

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The criterion for diagnosis of LE by plethysmography was a difference of ≥ 10% in volume between the upper limbs. The independent variables included age at the time of surgery, body mass index (BMI), postoperative complications (surgical wound dehiscence, seroma and infection), type of surgery, tumor stage, and postoperative adjuvant therapy.

The association between the qualitative variables and the presence of LE was analyzed with the Chi-square test or Fisher's exact test, depending on the expected values in the contingency table. The association between the quantitative variables and the presence of LE was analyzed with *Student's t* test for differences between mean values. Variables with *p*-values below 0.20 in the univariate analysis were submitted to multiple logistic regression. The level of statistical significance was set at 5% in all analyses.

The data were entered on an Excel spreadsheet and analyzed with the software SSPS (*Statistical Package for the Social Sciences*), version 18.0 for Windows. The study was previously approved by the ICC Research Ethics Committee.

RESULTS

The subjects included in the study (n = 325) were aged 51.9 years on the average (range: 26-68). LE secondary to surgery for BC was diagnosed in 101 subjects and absent in 224 (controls). Disease was stage I or II in most subjects (81.1%), with ductal carcinoma as the most common histological type (89.2%). The most frequent surgical procedure was mastectomy with lymphadenectomy up to the third level of Berg (83%). Only 9% of the patients were submitted to breast reconstruction, while 85% received postoperative radiotherapy. After the mammary bed, the most frequently irradiated areas were the axillary region, the supraclavicular fossa and the internal mammary chain.

In the univariate analysis, no difference was observed between LE patients and controls with regard to age and BMI. The average age was similar for the two groups (51.8 years; $p = 0.978$). The average BMI was 25.3 for LE patients and 26.7 for controls ($p = 0.062$).

The univariate analysis of the clinical and demographic data revealed that LE was associated with surgical wound dehiscence and infection (Table 1). Hormone therapy with tamoxifen ($p = 0.025$), irradiation of the supraclavicular fossa ($p = 0.002$) and adjuvant chemotherapy ($p = 0.003$) were also found to be associated with LE (Table 2). LE was more frequent in stages II, III and IV ($p = 0.007$) (Table 3).

Logistic regression identified three independent risk factors for LE: tumor stage (OR = 4.33; 95% CI; 1.19-15.66), surgical wound infection (OR = 7.85; 95% CI; 2.77-22.28) and irradiation of the supraclavicular fossa (OR = 2.90;

Table 1. Number and percentage of patients with and without lymphedema according to postoperative complication. Ceará Cancer Institute. January 2000-December 2007.

Variable	Category	Lymphedema No n (%)	Lymphedema Yes n(%)	*p*-value
Dehiscence	No	168 (66.4)	85 (33.6)	0.021
	Yes	55 (80.9)	13 (19.1)	
Seroma	No	184 (67.6)	88 (32.4)	0.095
	Yes	39 (79.6)	10 (20.4)	
Surgical wound infection	No	216(73.5)	78 (26.5)	< 0.001
	Yes	6(23.1)	20 (76.9)	
Complication	None	150 (69.4)	66 (30.6)	0.558
	One	48 (66.7)	24 (33.3)	
	Two	20 (80.0)	5 (20.0)	
	Three	4 (57.1)	3 (42.9)	

Table 2. Number and percentage of patients with and without lymphedema according to type of treatment. Ceará Cancer Institute. January 2000-December 2007.

Variable	Category	Lymphedema No n (%)	Lymphedema Yes n (%)	*p*-value
Type of surgery	Conservative	38 (69.1)	17 (30.9)	0.963
	Mastectomy	185 (68.8)	84 (31.2)	
Reconstruction	No	205 (69.3)	91(30.7)	0.678
	Yes	19 (65.5)	10 (34.5)	
Hormone therapy	No	54 (59.3)	37 (40.7)	0.020
	Yes	170 (72.6)	64 (27.4)	
Chemotherapy	No	156 (72.6)	59 (27.4)	0.240
	Yes	47 (65.3)	25 (34.7)	
Neoadjuvant chemotherapy	No	19 (55.9)	15 (44.1)	0.076
	Yes	203 (70.7)	84 (29.3)	
Adjuvant chemotherapy	No	13 (46.4)	15 (53.6)	0.003
	Yes	190 (73.4)	69 (26.6)	
Aromatase inhibitor	No	193 (68.2)	90 (31.8)	0.337
	Yes	31 (75.6)	10 (24.4)	
Tamoxifen	No	73 (61.3)	46 (38.7)	0.025
	Yes	151(73.3)	55 (26.7)	
Irradiation of mammary bed	No	32 (66.7)	16 (33.3)	0.726
	Yes	191 (69.2)	85 (30.8)	
Irradiation of axillae	No	148 (67.6)	71(32.4)	0.484
	Yes	75 (71.4)	30 (28.6)	
Irradiation of supraclavicular fossa	No	204 (71.8)	80 (28.2)	0.002
	Yes	19 (47.5)	21 (52.5)	
Irradiation of internal mammary chain	No	200 (68)	94 (32)	0.330
	Yes	23 (76.7)	7 (23.3)	

Table 3. Number and percentage of patients with and without lymphedema according to tumor stage and biomolecular aspects. Ceará Cancer Institute. January 2000-December 2007.

Variable	Category	Lymphedema		*p*-value
		No n (%)	Yes n (%)	
Tumor stage	I	28 (90.3)	3 (9.7)	0.059
	II	145 (66.5)	73 (33.5)	
	III	33 (66.7)	18 (33.3)	
	IV	3 (75)	1 (25.0)	
Tumor stage	I	28 (90.3)	3 (9.7)	0.007
	II-IV	184 (66.7)	92 (33.0)	
Histological type	Ductal	199 (68.6)	91 (31.4)	0.513
	Lobular	9 (81.8)	2 (1.2)	
Estrogen receptor	Negative	59	19.4	0.386
	Positive	245	80.6	
Progesterone receptor	Negative	98	53.3	0.122
	Positive	86	46.7	
c-ERB2	Negative	51	59.3	0.546
	Positive	35	40.7	
	Unknown	239	73.5	

Table 4. Risk factors for the development of lymphedema in patients submitted to surgery for breast cancer. Ceará Cancer Institute. January 2000-December 2007.

Variable	Category	Adjusted OR*	95% CI	*p*-value
Tumor stage	I	1.0	Reference	0.026
	II-IV	4.33	1.19-15.66	
Surgical wound infection	No	1.0	Reference	< 0.001
	Yes	7.85	2.77-22.28	
Irradiation of the supraclavicular fossa	No	1.0	Reference	0.007
	Yes	2.90	1.33-6.31	

* Variables adjusted for BMI, age and time from surgery to diagnosis of lymphedema (continuous variables); 95% CI 95%: Confidence interval.

95% CI; 1.33-6.31) (Table 4). The predictive score for LE corresponded to the cumulative number of risk factors (0-3) presented by each patient.

The prevalence of LE was found to be positively correlated with the predictive score: 0 (6.9%), 1 (26.1%), 2 (56.6%) and 3 (100%) (Table 5).

Table 5. Distribution of patients with and without lymphedema according to the number of cumulative risk factors identified in the logistic regression analysis. Ceará Cancer Institute. January 2000 - December 2007.

Number of cumulative risk factors (*)	No n (%)	Yes n (%)	*p*-value (**)
None	27 (93.1)	2 (6.9)	< 0.001
One	161 (73.9)	57 (26.1)	
Two	23 (43.4)	30 (56.6)	
Three	0 (0.0)	4 (100.0)	

* Risk factors: breast cancer of stage II or higher; infection of surgical wound; irradiation of the supraclavicular fossa. ** Chi-square test for linear trend.

DISCUSSION

Axillary dissection does not improve survival in BC patients, but a pathological examination of axillary lymph nodes is required to plan adjuvant therapy, and is effective at controlling regional disease.[10] The incidence of LE appears to be decreasing due to more conservative surgical treatment and earlier diagnostic; nonetheless, LE remains one of the most common complications after surgery for BC[8-20].

BC-related lymphedema is poorly understood and is further complicated by inconsistency among studies with regard to prevalence, incidence, risk factors, and prevention and treatment. In addition, LE continues to be underdiagnosed and has not yet been defined or measured in a standardized manner[3,15].

LE not only affects the quality of life, self image and functionality of the patient, but increases the risk of other complications, especially skin conditions like erysipelas, venous thrombosis and lymphangiosarcoma. The latter is a generally aggressive malignant tumor developing in approximately 1% of patients affected with LE in the limbs[10].

Risk factors for LE are not yet well established in the literature, but the condition is believed to be multifactorial. According to Kocak and Overgaard[11], risk factors may be related to either treatment, disease or patient characteristics. Treatment-related factors include surgical technique, radiotherapy, chemotherapy or a combination of these. Major disease-related factors include tumor stage and the number of affected lymph nodes[20]. Patient-related factors include demographic and clinical data such as age, comorbidities (e.g., high blood pressure), diabetes mellitus, obesity and surgical wound infection[10,12].

Advanced tumor stage at the time of diagnosis is an important predictive factor for LE[13]. Accordingly, in the present study LE was strongly associated with tumor stage II, III and IV, but less so with tumor stage I. Likewise, Rett[14] reported LE to occur on the average in 2.7% and 9.4% of cases diagnosed with stage I and II, respectively.

Although some studies[3] have shown that older age significantly increases odds of LE, in our univariate analysis, no correlation was observed between age and LE development. The same was true for BMI, although other authors[1,10,15,16] have reported obesity to be associated with LE. According to Paskett et al.[15] excessive weight imposes a burden on the lymphatic system, contributing to the development of LE.

Seroma tended towards, but did not reach, statistical significance in the present study, though sometimes considered a possible risk factor[15,16]. On the other hand, a clearly significant association between surgical wound infection and LE was observed in both the univariate and the multivariate analysis. Several authors have identified infection as a factor capable of triggering LE[17-19] within three to twelve months[14].

Radiotherapy following lymphadenectomy favors the development of LE[10,20,21]. In patients submitted to axillary radiotherapy, the amplitude of upper limb movement is reduced by 27% and the prevalence of LE is 18%. The corresponding figures for non-irradiated patients are 3% and 6%[21]. Another study[14] reported a relative risk of LE and changes in shoulder amplitude of 6.9% and 16.3%, respectively, in women submitted to irradiation of the mammary bed, axillary region and supra- and infraclavicular fossae. In this study, irradiation of the supraclavicular fossa was confirmed as a risk factor for LE, matching findings by Verves[22] who found irradiation of this region to increase the risk of LE by 3.6 times. Radiotherapy favors LE development probably by blocking the thoracic duct or the right lymphatic duct[9].

Based on three significant risk factors, the scoring system devised for this study proved to be a simple and practical tool for predicting LE and, thus, for making preventive and curative strategies capable of improving the quality of life of patients submitted to surgery for breast cancer.

CONCLUSION

In this study, three risk factors for development of LE were identified: tumor stage (II, III and IV), surgical wound infection and irradiation of the supraclavicular fossa. Based on these factors, a simple and useful LE prediction score was devised.

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